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Screening for Latent Tuberculosis Infection in Adults: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To review evidence about targeted screening for and treatment of latent tuberculosis infection (LTBI) among adults in primary care settings.

Data Sources: MEDLINE, the Cochrane Library, and trial registries through August 3, 2015; bibliographies from retrieved articles, outside experts, and reviewers, with surveillance of the literature through May 31, 2016.

Study Selection: Two investigators independently selected studies using a priori inclusion and exclusion criteria. We selected studies that evaluated the tuberculin skin test (TST) using the Mantoux method or tests evaluating commercial interferon-gamma release assays (IGRAs). We selected trials of treatment that evaluated pharmacotherapy regimens that are currently recommended by the Centers for Disease Control and Prevention for the treatment of LTBI for synthesis of benefits and harms. We excluded studies of persons with underlying immunosuppression and for whom LTBI screening and treatment would be part of standard disease management by specialty care providers (e.g., persons with HIV, history of or planned organ transplant, or planned or active use of tumor necrosis factor-alpha inhibitors). We excluded poor-quality studies, studies assessing specificity in countries with a high tuberculosis (TB) burden, and studies assessing harms and benefits in developing countries.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: We did not identify any studies that compared screening with no screening. We included 72 studies of fair to good quality; 67 assessed test accuracy or reliability and five assessed benefits and harms of treatment. Pooled estimates for sensitivity of TST at both the 5-mm and 10-mm induration thresholds for positivity were 0.79; the pooled estimate at the 15-mm threshold was 0.52. Pooled estimates for sensitivity of IGRA tests ranged from 0.77 to 0.90. Estimates for specificity of TST at the 5-mm threshold varied considerably by TB burden of the study setting (0.94 to 0.97 in low-burden countries and 0.30 in an intermediate-burden country). Pooled estimates for specificity at the 10-mm and 15-mm thresholds were 0.97 and 0.99, respectively. Pooled estimates for specificity of IGRA tests ranged from 0.95 to 0.98. We found evidence for at least moderate interrater reliability for both TST and IGRA tests.

The best evidence on effectiveness of treatment of LTBI was from the International Union Against Tuberculosis (IUAT) trial, a large (N=27,830) good-quality randomized, controlled trial (RCT) that evaluated multiple treatment durations for daily isoniazid. It found a relative risk (RR) for progression to active TB at 5 years of 0.35 (95% confidence interval [CI], 0.24 to 0.52) for 24 weeks of isoniazid compared with placebo (N=13,955; number needed to treat, 112). Our sensitivity analyses adding four RCTs that did not meet all of our eligibility criteria (e.g., compared isoniazid with placebo using a longer duration of treatment or used different doses than currently recommended) found an RR of 0.31 (95% CI, 0.24 to 0.41; I^2=0%; 5 RCTs, N=36,823). A head-to-head, open-label, noninferiority RCT that compared a combination of once-weekly rifapentine plus isoniazid for 3 months with daily isoniazid for 9 months found the combination therapy to be noninferior to isoniazid alone for preventing the development of

active TB.

For harms, the IUAT trial reported an RR for hepatotoxicity of 4.59 (95% CI, 2.03 to 10.39; number needed to harm [NNH], 279) for 24 weeks of isoniazid compared with placebo. Sensitivity analyses pooling the IUAT with three RCTs that used a longer duration of isoniazid yielded a similar result (pooled RR, 5.04 [95% CI, 2.50 to 10.15]; I^2=0%; 4 RCTs, N=35,161). The RR of treatment discontinuation because of adverse effects across all treatment duration arms in IUAT was 1.50 (95% CI, 1.18 to 1.89; N=27,830; NNH, 167). For isoniazid compared with rifampin, the pooled RR for hepatotoxicity was 3.29 (95% CI, 1.72 to 6.28; I^2=0%; 3 RCTs, N=1,327) and the pooled RR for treatment discontinuation because of adverse events was 1.61 (95% CI, 0.57 to 4.57; I^2=40.0%; 3 RCTs, N=1,327).

Limitations: No test for the direct diagnosis of LTBI exists; thus, studies of test accuracy use subjects with confirmed active TB to establish sensitivity and healthy, low-risk subjects to establish specificity. Thus, applicability to other populations is uncertain. The single trial meeting all eligibility criteria that established the benefits of a currently recommended treatment (isoniazid 300 mg daily for 24 weeks) for preventing active TB was published more than 30 years ago and was conducted among subjects with pulmonary fibrotic lesions; whether it may overestimate the benefits of treatment for populations with lower risk for progression is not clear. No trials evaluated the effectiveness (compared with placebo) of regimens other than isoniazid. Contemporary treatment studies have not included placebo arms; when available, information on benefits and harms of newer treatments are derived from comparative studies (vs. isoniazid). The evidence on harms is limited by heterogeneous specification of outcomes across studies. This review is not applicable to persons with the highest risk, for whom testing and treatment is considered part of disease management or public health surveillance.

Conclusions: We did not find any studies evaluating the direct benefits and harms of screening for LTBI in the adult populations and settings included in this review. Both types of currently available tests (TST and IGRA) are moderately sensitive and, within countries with a low TB burden, highly specific. Isoniazid treatment reduces the risk of progression to active TB in persons with LTBI and pulmonary fibrotic lesions. The evidence is limited or not available for other regimens and outcomes (e.g., deaths due to TB, all-cause mortality) among the populations included in this review. Isoniazid is associated with higher rates of hepatotoxicity than placebo and rifampin regimens.

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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) last made a recommendation on latent tuberculosis (TB) screening in 1996. With new tests and treatments for latent TB infection (LTBI), an updated assessment of the evidence to inform recommendations on screening is warranted.

The purpose of this report is to systematically review the current evidence on targeted screening for and treatment of LTBI in populations and settings relevant to primary care in the United States. In this report, we summarize the evidence on the benefits and harms of screening for LTBI in selected high-risk adult populations, the test characteristics of U.S. Food and Drug Administration (FDA)-approved screening tests, and the benefits and harms of Centers for Disease Control and Prevention (CDC)-recommended treatments for LTBI. This review also identifies key gaps in this scientific literature.

This review was scoped to provide the USPSTF with answers to key questions (KQs) needed to inform a recommendation about LTBI screening in asymptomatic, generally healthy adults in settings relevant to primary care. Thus, the review does not focus on the testing of close contacts of persons with active TB or medically vulnerable populations for whom LTBI testing is considered part of disease management. Further, this review does not focus on important issues related to TB epidemiology, such as risk of transmission, the public health infrastructure for TB, or adherence to all steps involved in testing and treatment.

Condition Definition

TB is a disease caused by *Mycobacterium tuberculosis* that is spread through airborne transmission. TB usually affects the lungs but can also affect other parts of the body, such as the brain, kidneys, or spine. When a person with active pulmonary TB coughs or sneezes, droplet nuclei containing *M. tuberculosis* are expelled into the air. If another person inhales air containing these droplet nuclei, three conditions are possible: clearance of the organism; onset of active disease (primary TB disease); or latent infection without signs, symptoms, or radiographic or bacteriologic evidence of TB disease.[1] Persons with LTBI are not infectious to others. LTBI can later reactivate when previously dormant *M. tuberculosis*, seeded at the time of exposure, proliferate and progress to cause active TB disease.

Etiology and Natural History

After exposure to *M. tuberculosis*, approximately 30 percent of persons are thought to develop LTBI, as diagnosed based on a positive tuberculin skin test (TST).[2,3] Five to 10 percent of healthy (immunocompetent) persons with a positive TST will progress from LTBI to active TB disease (referred to as reactivation) in their lifetime. This estimate is based on epidemiologic data

and data from placebo arms of treatment trials conducted before treatment of LTBI was routinely recommended.[4,5] However, this range underestimates the risk of progression to active TB for some patients and overestimates the risk for others, because risks vary greatly according to age, the size of the TST reaction, and the presence or absence of specific medical conditions.[6]

A recently published observational study of contacts of persons with active TB in Amsterdam who were diagnosed with LTBI between 2002 and 2011 reported a 5-year risk of incident TB of 2.4 percent (95% confidence interval [CI], 1.2 to 4.7) among those who did not take preventive therapy.[7] A recent report using 2006–2008 U.S. data estimated the rate of TB reactivation among persons with LTBI as 0.084 cases per 100 person-years (95% CI, 0.083 to 0.085).[8] Among persons who tested positive versus negative for HIV, rates were 1.82 (95% CI, 1.74 to 1.89) and 0.073 (95% CI, 0.070 to 0.075) cases per 100 person-years, respectively. Reactivation rates were higher among foreign-born persons (0.098 cases per 100 person-years [95% CI, 0.096 to 0.10]) than among those born in the United States (0.082 cases per 100 person-years [95% CI, 0.080 to 0.083]).

Risk Factors

Persons may be considered "high risk" for LTBI for several reasons.[1,9,10] Some may be high risk because of increased likelihood of exposure to active TB. Others may be high risk because of increased likelihood of latent infection if exposed because of medical conditions or other factors that influence the immune system. Some persons with increased chance of latent infection due to underlying immune factors may also have an increased risk of LTBI reactivation. The estimates for prevalence of LTBI among some higher-risk populations and estimates for risk of reactivation of LTBI are frequently based on older studies that may not correspond to current risks and practice patterns.

Risks for incident LTBI associated with increased exposure to active TB include being born outside the United States, having lower household income or less than a high school education, being male, being a member of a racial/ethnic minority population, being an active smoker, and living with someone with active TB.[11] Substantially increased exposure to active TB has also been observed among homeless persons, injection drug users, persons with HIV, and residents or employees of a high-risk congregate setting (e.g., prison, long-term care facility, hospital, homeless shelter).[9]

Risks associated with a higher likelihood of latent infection if exposed, reactivation to active TB, or both vary.[9] These risks include HIV infection, injection drug use, radiographic evidence of prior healed TB, low body weight (10% below ideal), and certain medical conditions (e.g., silicosis, poorly controlled diabetes mellitus, chronic renal failure, gastrectomy, solid organ transplant, smoking, head and neck cancer, and conditions that require prolonged use of corticosteroids or other immunosuppressive agents).[1,6,9,10] However, there is uncertainty in the estimated risk of developing active TB in persons with these conditions. One review found that estimates of the relative risk (RR) of developing active TB in persons with medical conditions that impair the host's immune system are either lower than expected or have significant methodological flaws (e.g., failure to distinguish among the risk of exposure, risk of infection, and risk of reactivation; small sample sizes).[6] This same review offers RR estimates for

reactivation to active TB for a number of high-risk populations; the two populations most relevant to primary care settings are Hispanic patients with poorly controlled diabetes (RR, 1.7 [95% CI, 1.5 to 2.2]) and smokers (RR 1.5 [95% CI, 1.1 to 2.2]).[12]

Prevalence and Burden

The prevalence and burden of active TB disease affects the prevalence and burden of LTBI. TB is a substantial health issue globally, with nearly 9 million cases of active TB and 1.5 million TB-related deaths worldwide in 2013.[13] In the United States, active TB is a much more limited health problem, with cases declining in recent decades. In 2015, a total of 9,536 new active TB cases were reported in the United States, corresponding to an incidence rate of 3.0 cases per 100,000 population.[14] There were 555 deaths from TB disease in the United States in 2013, the most recent year for which these data are available.[15] The proportion of TB deaths occurring among HIV-infected persons compared with non–HIV-infected persons is difficult to estimate because deaths among coinfected persons are typically attributed in vital statistics to HIV infection, as opposed to TB disease. Further, HIV status is unknown in some active TB cases.[16,17] In 2014, the prevalence of unknown HIV status among TB cases was 14 percent and the prevalence of HIV among cases of active TB with known HIV status was 6.3 percent.[18]

Among persons with known national origin, 6,335 active TB cases were among foreign-born persons (66.2% of all cases) in 2015, for a rate of 15.1 cases per 100,000 population compared with 1.2 cases per 100,000 population among U.S.-born persons.[14] Active TB rates also vary by race/ethnicity; rates per 100,000 U.S.-born population in 2015 were 0.7, 2.0, 2.0, 4.0, 8.4, and 6.8 among non-Hispanic whites, Hispanics or Latinos, Asians, non-Hispanic blacks or African Americans, Native Hawaiians or other Pacific Islanders, and American Indians or Alaska Natives, respectively.[14] Rates per 100,000 foreign-born U.S. population in 2015 were 3.7, 11.5, 29.9, and 27.7 among non-Hispanic whites, Hispanics or Latinos, Asians, and non-Hispanic blacks or African Americans, respectively. The incidence of active TB varies significantly by geographical location (state) within the United States: California, Texas, New York, and Florida combined accounted for more than half of all U.S. TB cases reported in 2015.[14] Among persons with active TB age 15 years or older in 2014, 5.5 percent were homeless, 2.2 percent were long-term care facility residents, and 4.2 percent were in a correctional facility.[18]

Estimating the prevalence of LTBI overall and among higher-risk groups is challenging because no direct test for latent *M. tuberculosis* exists and latent infection is not reportable to the CDC's National Notifiable Disease Surveillance System.[19] Unlike active TB disease, which is diagnosed on the basis of clinical signs and symptoms and confirmed by bacteriologic or molecular identification of *M. tuberculosis* from fluid or tissue specimens, existing tests for latent infection measure memory T cell response, an indirect measure of host sensitization to *M. tuberculosis*.[10] In general, estimates of the prevalence of LTBI are based on studies using TST and/or interferon-gamma release assay (IGRA) to define infection.

The largest prevalence studies use data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the civilian, noninstitutionalized U.S. population, to estimate the prevalence of LTBI based on an induration of 10 mm or larger on

TST or a positive IGRA. Using 2011–2012 NHANES data, the population prevalence of LTBI among persons age 6 years or older is 4.7 percent (95% CI, 3.4 to 6.3) based on a positive TST alone, 5.0 percent (95% CI, 4.2 to 5.8) based on a positive IGRA alone, and 2.1 percent (95% CI, 1.5 to 2.8) based on a positive TST and IGRA. Among the foreign-born U.S. population age 6 years or older, the prevalence of LTBI is 20.5 percent (95% CI, 16.1 to 25.8) based on a positive TST alone, 15.9 percent (95% CI, 13.5 to 18.7) based on a positive IGRA alone, and 9.3 percent (95% CI, 7.4 to 11.7) based on a positive TST and IGRA.[20] Other than foreign-born persons, NHANES does not include enough persons at higher risk for TB in the sample; thus, nationally representative population estimates among higher-risk groups other than foreign-born persons are not available.

Published estimates of LTBI prevalence among higher-risk groups may have limited generalizability based on the specific population(s) used to collect the estimates, the number of participants included, the tests and definitions for a positive test, and whether studies were conducted within a single or multicenter setting. For example, a retrospective study estimated the LTBI prevalence among the homeless New York City population over the years 1992 to 2005 to be 27.1 percent based on convincing self-reported history of positive TST, but prevalence based on actual testing with TST (threshold for positivity was not specified) was 12.5 percent.[21] A review published in May 2015 offers LTBI prevalence and active TB disease incidence estimates by high-risk categories based on studies published in English, French, or Spanish between 2009 and 2014. These estimates vary by test used (TST or IGRA) and in some cases are based on a single study. These estimates are summarized in **Appendix A Table 1**.[10]

Rationale for Screening

The prevention of active TB by treating LTBI is a major goal of the national strategy for eliminating TB in the United States.[22,23] The CDC does not recommend universal or untargeted population screening for LTBI. That is, the CDC discourages the use of tests for LTBI among persons and populations at low risk for TB infection, and discourages a testing approach that is independent of a risk assessment.[1] Rather, the CDC recommends screening for LTBI among population subgroups with higher prevalence of LTBI (i.e., prevalence substantially greater than that of the general U.S. population) or in persons who have increased risk of progression from LTBI to active TB disease.

Screening Strategies

For the purposes of this review, we define screening as the use of a test in asymptomatic persons for the purpose of identifying candidates for medication to prevent progression to active TB. No direct test for the presence of latent *M. tuberculosis* is available as a reference standard for LTBI screening tests. The diagnosis of LTBI is based on medical and social history, physical examination, and TST or IGRA results (both discussed below). The presence of active TB disease should be excluded before treatment of LTBI is initiated; failure to do so may result in inadequate treatment and development of drug resistance.[1] Chest x-ray is often recommended in patients who have a positive screening test for LTBI, along with a symptom questionnaire to help differentiate LTBI and active TB disease.

TST

TST is administered by injecting 0.10 mL of an intermediate-strength dose of purified protein derivative (PPD) intradermally using the Mantoux technique, with interpretation within 48 to 72 hours. In the United States, an intermediate-strength dose is 5 tuberculin units (TU) of PPD-S. In other countries, PPD RT-23 is used, and an approximately equivalent intermediate-strength dose is 2 to 2.5 TU.[24,25] If a person is infected with TB, a delayed-type hypersensitivity reaction is typically detectable 2 to 8 weeks after initial infection. Health care providers should be trained in the administration and interpretation of TST.[9]

Based on the sensitivity and specificity of the TST and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive reaction: 5 mm or larger, 10 mm or larger, and 15 mm or larger of induration.[1,9] A TST reaction of 5 mm or larger of induration is considered positive in persons with the highest risk of developing active TB: patients with HIV infection; patients with organ transplants and other immunosuppressed patients (e.g., patients taking the equivalent of ≥15 mg/day of prednisone for 1 month or those taking tumor necrosis factor-alpha antagonists); patients with recent contact with a person who has infectious TB disease; or persons with fibrotic changes on a chest x-ray consistent with prior TB. A TST reaction of 10 mm or larger of induration is considered positive for LTBI in the following persons: recent arrivals to the United States (within the last 5 years) from countries with a high TB prevalence; injection drug users; residents or employees of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, hospitals and other health care settings, residential facilities for persons with HIV infection, and homeless shelters); and persons with clinical conditions that increase the risk of progression to TB disease.[1] A TST reaction of 15 mm or larger of induration is considered positive in persons with no known risk factors for TB.[1,9]

IGRAs

IGRAs are performed using fresh, whole-blood specimens. Blood is mixed with assay peptides that simulate antigens derived from *M. tuberculosis*. If infected with *M. tuberculosis*, white blood cells recognize the simulated antigens and release interferon-gamma. Currently, two FDA-approved IGRAs are commercially available: QuantiFERON-TB® Gold In-Tube (QFT-GIT) (Qiagen, Germantown, MD), approved by the FDA in 2007, and T-SPOT.*TB*® (Oxford Immunotec Global, Marlborough, MA), approved by the FDA in 2010.[1,26] The antigens used by both commercially available tests (ESAT-6 and CFP-10) are absent in the bacille Calmette–Guérin (BCG) vaccine and most nontuberculosis mycobacteria. QFT-GIT was approved as a modification to the second-generation test approved in 2005 (QuantiFERON-TB Gold [QFT-G]) and includes an additional antigen (TB7.7).

The interpretation of IGRA tests is based on the measured amount of interferon-gamma released (QFT-G and QFT-GIT) or on the number of visible spots that form in response to cells that release interferon-gamma (T-SPOT.*TB*). The CDC recommends that laboratories provide both the qualitative and quantitative results. Qualitative results are reported as positive, negative, indeterminate, or borderline. Quantitative results are reported as numerical values that include a response to the TB antigen and two controls (nil and mitogen). Quantitative results may be useful for clinical decisionmaking in individual cases, in combination with risk factors. IGRAs have

some advantages over TST. They require a single patient visit to conduct the test, results can be available within 24 hours, they do not cause a "booster phenomenon," and they are unaffected by BCG vaccination and most environmental mycobacteria.[1] However, blood samples must be processed relatively quickly (within 8 to 30 hours after collection), and limited data exist in certain groups (e.g., persons recently exposed to TB, immunocompromised persons, and persons who will be tested repeatedly).

Among persons at higher risk for TB, the CDC considers IGRAs the preferred method of testing for groups who have poor rates of return for TST reading and interpretation (e.g., homeless persons) and persons who have received BCG vaccination.[1] The CDC indicates that either TST or IGRAs can be used for other high-risk persons. The CDC does not recommend routine testing with both TST and IGRAs but suggests situations where results from both tests could be useful. For example, IGRA testing might follow a positive TST among persons who have a low risk of both infection and progression from infection to TB disease, or follow a negative TST when the risk for infection, progression to disease, and/or a poor outcome is high, such as among HIV-infected persons.[1]

Because no direct test for LTBI infection exists, the test characteristics for both TST and IGRAs are difficult to establish for latent infection. Sensitivity is generally extrapolated from the sensitivity of these tests in populations with active TB. Similarly, specificity is generally extrapolated from evaluating the test within populations of healthy persons, free of TB risks or exposures, and without underlying medical conditions that increase risk for TB infection.

Treatment Approaches

Persons who screen positive for LTBI and in whom active infection has been excluded are generally offered treatment with antituberculosis medications.[9] For decades, isoniazid was the only medication used for treating LTBI. However, concerns about adverse events, primarily hepatotoxicity, and difficulty with patient adherence to long treatment regimens prompted the evaluation of alternative regimens.

The American Thoracic Society, the CDC, and the Infectious Diseases Society of America recommend several regimens for treating LTBI; these regimens vary by drug, dose frequency, and duration of treatment.[27] The regimens include isoniazid and drugs in the rifamycin class (rifampin and rifapentine). In 2011, the CDC issued additional recommendations based on findings from three randomized, controlled trials (RCTs) that demonstrated that a weekly regimen with isoniazid and rifapentine for 12 weeks was as effective as traditional 6- or 9-month isoniazid regimens for healthy persons.[28] The recommended regimens for treating LTBI in adults are summarized in **Appendix A Table 2**.

Current Clinical Practice in the United States

Current guidelines from several organizations reflect a movement toward targeted testing and treatment. In developed countries with a low prevalence of TB such as the United States, most

authorities recommend that LTBI screening be done only among high-risk groups and when treatment is feasible. In 2005, the CDC, in collaboration with the American Thoracic Society and the Infectious Diseases Society of America, issued its most recent joint recommendations for controlling TB.[27] In 2011, the CDC convened an expert panel to review evidence from new trials that resulted in a recommendation for a new alternative regimen (weekly isoniazid/rifapentine for 12 weeks).[27,28] In 2015, the World Health Organization released new guidelines on the management of LTBI that offer a public health approach for testing, treating, and managing LTBI primarily geared toward high- and upper middle-income countries.[29] These guidelines recommend testing for and treatment of LTBI in persons at the highest risk of progression to active disease, including persons with HIV, close contacts of persons with active pulmonary TB, and patients with selected conditions or those undergoing treatment commonly associated with immunosuppression (e.g., transplant, antitumor necrosis factor treatments).

Estimates for the current prevalence of screening for LTBI in primary care settings are not available. Further, estimates of the proportion of high-risk groups and persons cared for in primary care settings are difficult to determine and likely vary by the type of primary care setting (e.g., a public health clinic or safety net provider in a region of the United States with a high TB burden vs. a private primary care practice in a community with a low TB burden).

Previous USPSTF Recommendation

In 1996, the USPSTF recommended screening with TST in asymptomatic high-risk persons (A recommendation) and BCG vaccination only for selected high-risk persons (B recommendation). Prior to the present update, the USPSTF Web site referred to the CDC for this recommendation, stating, "The USPSTF recognizes the importance of targeted screening for tuberculosis. However, the USPSTF does not wish to duplicate the work of the Centers for Disease Control and Prevention (CDC) in this area and will not update its 1996 recommendations."

Chapter 2. Methods

KQs and Analytic Framework

The Evidence-based Practice Center investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and KQs for this review. The analytic framework illustrates the KQs that guided the review (**Figure 1**).

1. Is there direct evidence that targeted screening for LTBI in primary care settings in asymptomatic adults at increased risk for developing active TB disease (e.g., individuals in populations with a high prevalence of active TB disease or with documented increased risk for progression from LTBI to active TB disease) improves quality of life or reduces active TB disease incidence, transmission of TB, or disease-specific or overall mortality?

2a. What is the accuracy and reliability of the TST or IGRA for screening asymptomatic adults who are at increased risk for developing active TB disease?

2b. What is the accuracy and reliability of sequential screening strategies that include both TST and IGRA testing in asymptomatic adults who are at increased risk for developing active TB disease?

3. Does treatment of LTBI with CDC-recommended pharmacotherapy regimens improve quality of life or reduce progression to active TB disease, transmission of TB, or disease-specific or overall mortality?

4. Are there harms associated with screening for LTBI?
   a. Do these harms differ by screening method or strategy?
   b. Do these harms differ by population?

5. Are there harms associated with treatment of LTBI with CDC-recommended pharmacotherapy regimens?

Data Sources and Searches

With the assistance of a librarian with extensive experience conducting searches in support of systematic reviews, we searched PubMed/MEDLINE and the Cochrane Library for English-language articles published through August 3, 2015. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. Complete search terms and limits are listed in **Appendix B1**. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies that met our inclusion criteria, and added all previously unidentified relevant articles. We reviewed all studies suggested by peer reviewers or public comment respondents and, if appropriate, incorporated them into the final review. Since August 2015, ongoing surveillance has been conducted through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on May 31, 2016, and no new studies

were identified.

Study Selection

We developed inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs (**Appendix B2**). We excluded studies in which more than 25 percent of the study population was younger than age 18 years or known to be HIV positive, unless results were stratified by these characteristics. For KQ 1, we included RCTs or prospective cohort studies that compared screening with no screening in primary care settings and focused on asymptomatic adults belonging to populations at increased risk for developing active TB (e.g., injection drug users, persons who are homeless or residing in homeless shelters, former prisoners, persons born in or former residents of countries with high TB prevalence, and persons who work with such individuals). We excluded studies of close contacts of persons with active TB because testing and treatment of such populations is considered part of contact tracing for public health as opposed to a primary care function. We also excluded studies of persons with underlying immunosuppression and for whom LTBI screening and treatment would be part of standard disease management by specialty care providers (e.g., persons with HIV, head and neck cancer, leukemia or lymphoma, silicosis, history of or planned organ transplant, planned or active use of tumor necrosis factor-alpha inhibitors, and planned or active use of chemotherapy) because testing and treatment typically need to be individualized and managed with respect to the patient's comorbidities and medication regimens.

For KQ 2, because there is no direct test for LTBI,[26] we relied on data from studies of persons with bacteriologic-confirmed, active TB to determine sensitivity or studies of healthy subjects known to be at low risk for TB and free of TB exposure to determine specificity. We included studies assessing the accuracy or reliability of three IGRAs (T-SPOT.*TB*, QFT-G, and QFT-GIT) using the commercially specified threshold but also reported results based on other thresholds when available. For studies assessing the accuracy of the TST using the Mantoux method, we required the use of intermediate-strength PPD. Systematic reviews or primary studies of test accuracy were eligible for KQ 2.

For KQs 3 and 5, we included RCTs of persons with LTBI comparing a CDC-recommended treatment (medication, dose, and duration) with placebo, delayed treatment, no treatment, or another CDC-recommended treatment. For KQ 5, prospective cohort studies and case-control studies were also eligible. For KQ 4, systematic reviews, RCTs, and prospective cohort studies reporting false-positive results leading to unnecessary testing (e.g., chest x-ray) or treatment, labeling, stigma, anxiety, or cellulitis were eligible.

For KQs 1, 3, 4, and 5, we included studies conducted in primary care settings in countries categorized as "very high" on the Human Development Index (as defined by the United Nations Human Development Programme). We defined primary care broadly to include public health settings or specialized clinics providing primary care functions (e.g., prison clinics). For KQ 2 sensitivity outcomes, we did not set any exclusion criteria based on setting or country; for KQ 2 specificity outcomes, we excluded studies conducted in countries with a high TB burden as defined by the World Health Organization (**Appendix B2**).[30]

Two investigators independently reviewed titles and abstracts; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. Two investigators independently reviewed the full text to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. A second team member reviewed all data extractions for completeness and accuracy.

We assessed the quality of studies as good, fair, or poor using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B3**).[31] Two independent reviewers assigned quality ratings for each study. Disagreements were resolved by discussion with an experienced team member. For our main analyses, we included only studies rated as having good or fair quality.

Data Synthesis and Analysis

We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in tabular or narrative format. To determine whether meta-analyses were appropriate, we assessed both the number of studies available and the clinical and methodologic heterogeneity of the studies following established guidance.[32] To do this, we qualitatively assessed the populations, similarities and differences in screening tests or treatments used, and similarities in outcomes and timing of outcomes assessed.

For KQ 2, when at least three similar studies were available, we conducted quantitative synthesis of studies with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to determine pooled estimates of sensitivity and specificity.[33] We generated pooled estimates by test for sensitivity and stratified by important covariates, such as the timing of testing with respect to when pharmacotherapy for TB was started,[26] the prevalence of HIV among the study population, the TB burden in the country where the study was conducted, and, for T-SPOT.*TB*, the threshold used for positivity (FDA or European threshold).[34,35] For specificity, we also generated pooled estimates by test and stratified by important covariates such as the prevalence of BCG vaccination in the study population and the TB burden of the country in which the study was conducted. For T-SPOT.*TB*, we also generated estimates stratified by the threshold for positivity. We qualitatively summarized reliability outcomes and sensitivity and specificity outcomes for some tests or induration thresholds using tables and narrative because we did not have a sufficient number of studies to conduct quantitative syntheses.

We conducted several types of sensitivity analyses. First, because DerSimonian and Laird random-effects models may not perform well for small meta-analyses (when few studies are included), we conducted sensitivity analyses using maximum likelihood random-effects

methods.[36-40] Results were essentially the same as for our main analyses, with some minor variation in width of CIs for some estimates. Therefore, the results from these analyses are only provided in the appendix and are not discussed in the text. Next, we did not include studies rated as poor quality in any main analyses but did include them in sensitivity analyses for KQ 2.

For KQ 3 and for most comparisons and outcomes related to KQ 5, we did not conduct meta-analyses for our main analysis because we did not have a sufficient number of studies meeting all eligibility criteria that made the same comparison and reported similar outcomes. Therefore, we synthesized the included studies qualitatively, using narrative and tables. We calculated the RR for outcomes of interest (e.g., development of active TB disease, mortality from TB, development of hepatotoxicity) using the number of all randomized patients as the denominator to reflect a true intention-to-treat analysis. For our main analyses for KQ 5, we conducted quantitative synthesis of RCTs comparing isoniazid with rifampin for the following outcomes: hepatotoxicity and discontinuation due to adverse events. For sensitivity analyses for KQs 3 and 5, we conducted quantitative synthesis of RCTs by adding excluded studies that compared isoniazid with placebo that met many of our inclusion criteria but used a longer duration of treatment than is currently recommended (e.g., ≥1 year of isoniazid),[41-44] used lower or higher doses than currently recommended,[42,43] or did not require LTBI confirmation for subjects to be eligible.[41,43,44] For RCTs to be included in sensitivity analyses, we required that they either confirmed LTBI for subjects to be eligible (e.g., by enrolling only those who were tuberculin positive), reported data for subjects with confirmed LTBI (e.g., for the tuberculin-positive subset of subjects), or that the vast majority of subjects (>75%) were tuberculin positive. For these analyses, we used random-effects models with the inverse-variance weighted method (DerSimonian and Laird) to estimate RRs.[45] We conducted quantitative synthesis for the following outcomes: development of active TB disease, hepatotoxicity (e.g., isoniazid-induced hepatitis), and discontinuation of treatment due to adverse events. Because DerSimonian and Laird random-effects models may not perform well for small meta-analyses (when few studies are included), we also conducted sensitivity analyses using profile likelihood random-effects methods.[36-40] Results were essentially the same as for those using DerSimonian and Laird random-effects models, with some minor variation in width of CIs for some estimates.

For all quantitative syntheses, the chi-squared statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess statistical heterogeneity in effects between studies.[46,47] An I^2 from 0 to 40 percent might not be important, 30 to 60 percent may represent moderate heterogeneity, 50 to 90 percent may represent substantial heterogeneity, and 75 to 100 percent represents considerable heterogeneity.[48] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence for heterogeneity (e.g., p-value from the chi-squared test or a CI for I^2). However, as precision and the number of subjects increase, I^2 may become inflated toward 100 percent and may not reflect clinically relevant heterogeneity.[49]

All quantitative analyses were conducted using Stata® version 13.1 (StataCorp, College Station, TX).[50]

Expert Review and Public Comment

The draft analytic framework and draft research questions were made available for public comment and subsequently revised. A draft of this report was made available for public comment and reviewed by content and methodologic experts, USPSTF members, CDC experts, and AHRQ Medical Officers. It was revised based on comments received.

USPSTF and CDC Involvement

This review was cofunded by AHRQ and the CDC. AHRQ and CDC staff and members of the USPSTF participated in developing the scope of the work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 4,408 unique records and assessed 614 full-text articles for eligibility (**Figure 2**). We excluded 541 studies for various reasons detailed in **Appendix C** and we included 72 published studies of good or fair quality in our main analyses (**Appendix D**). Of the included studies, 67 were primary studies of screening test characteristics (KQ 2a). Three studies were RCTs focused on the benefits (KQ 3) and five studies were focused on the harms (KQ 5) of pharmacotherapy for the treatment of LTBI. We identified no eligible studies for KQ 1 (direct evidence for screening for LTBI) or KQ 4 (harms of screening). Details of quality assessments are provided in **Appendix E**.

Results by KQ

KQ 1. Direct Evidence for Targeted Screening for LTBI

We found no eligible studies that addressed this question.

KQ 2a. Accuracy and Reliability of Screening Tests

We identified 67 observational studies of good or fair quality assessing the sensitivity, specificity, or reliability of one or more of the included screening tests.

Sensitivity of Screening Tests

We relied on evidence from 50 primary studies of good or fair quality in subjects with bacteriologic-confirmed, active TB because no reference standard for direct diagnosis of LTBI exists.[51-100]

Study Characteristics

Thirteen studies estimated sensitivity for TST,[51-55,57,62,69,70,73-75,98] 16 studies for T-SPOT.*TB*,[56,60,61,64,67,69,71,75,78-80,82,83,86-88] 16 studies for QFT-G,[55,56,59,65-72,77,84,85,87,88] and 24 studies for QFT-GIT.[51,57,58,63-65,73,74,76,81,83,86,88-96,98-100] Characteristics of studies are provided in **Appendix D Tables 1** (TST) and **2** (IGRA). One study started using QFT-G but converted to using QFT-GIT midway through the study.[97] Eight studies estimating sensitivity were conducted in countries with a high TB burden,[51,57,58,63,76,78,95,96] 29 were conducted in countries with an intermediate TB burden,[55,64-73,75,79-85,88-94,97,98,100] and 10 were conducted in countries with a low TB burden,[52-54,56,59-62,74,77] including four in the United States. Three multinational studies were conducted in a mix of low- and intermediate-burden countries.[86,87,99] Sixteen studies were conducted in countries with a Human Development Index of less than "very high."[51,57,58,63,69,70,75,76,78,82,83,87,90,91,95,96] Twenty-nine studies provided stratified results for the HIV-negative segment of their study

population or excluded patients with HIV from the study population.[51,53-57,60,62-64,66-70,73,74,76,77,80,81,85,88,89,91,92,95,96,98] Three studies were conducted in a study population in which less than 25 percent of the study participants had received BCG vaccination.[58,76,77] Thirteen studies included between 25 and 75 percent vaccinated populations[54,55,57,62,63,65,67,68,72,74,91,93,94] and 12 studies included more than 75 percent vaccinated populations.[51,56,69-71,75,84,85,87,95,96,98] Twenty-two studies did not report the BCG vaccination prevalence in the study population. The timing of testing with respect to starting antituberculosis treatment varied across studies by the following categories: prior to or within 7 days (20 studies),[53,56,57,62,63,65,67,69-71,74,76,77,81,84,87,92,95,96,100] within 14 days (four studies),[59,60,64,86] within 30 days (one study),[75] or not reported (25 studies).[51,52,54,55,58,61,66,68,72,73,78-80,82,83,85,88-91,93,94,97-99]

Results

We calculated pooled estimates for sensitivity of TST by induration threshold and of IGRA by assay (**Table 1**; **Figures 3** and **4**). The pooled sensitivity of TST was 0.79 (95% CI, 0.69 to 0.89; I^2=94.6%) for a 5-mm threshold, 0.79 (95% CI, 0.71 to 0.87; I^2=91.4%) for a 10-mm threshold, and 0.52 (95% CI, 0.35 to 0.68, I^2=95.5%) for a 15-mm threshold. For the T-SPOT.*TB* IGRA, we found no difference in estimates based on whether the FDA or European threshold for positivity was used, so we combined all studies for a pooled estimate of 0.90 (95% CI, 0.87 to 0.93; I^2=63.6%) (**Appendix F Figure 19**). We found lower estimates for sensitivity of the QFT tests; the pooled estimate for sensitivity of QFT-G was 0.77 (95% CI, 0.74 to 0.81; I^2=55.3%) and was 0.80 (95% CI, 0.77 to 0.84; I^2=74.3%) for QFT-GIT. The percent of IGRA tests with indeterminate results ranged from 3 to 7 percent in studies reporting this information.

In a sensitivity analysis, we added the 14 studies[81,85,101-112] that were excluded for poor quality and found that estimates did not appreciably change (**Appendix D Tables 5** and **6**; **Appendix F Figures 1** and **2**). We repeated all analyses using a maximum likelihood–based method for random effects and found similar results, except for a slightly higher point estimate for TST at a 5-mm threshold (**Appendix F Figures 4** and **5**).

Because we found moderate to substantial statistical heterogeneity, we stratified results for all tests based on factors that were consistently reported across studies and could impact the accuracy of the test (**Appendix F Figures 7–31**). Factors that might lower sensitivity include testing that occurs after antituberculosis treatment has been started and higher proportion of study subjects with HIV or other immunosuppressing conditions. Other factors that might affect accuracy include country TB burden and BCG vaccination prevalence among the study population. Our analyses stratified by these two factors were similar because the prevalence of BCG vaccination among the study population is often correlated with the country's TB burden; BCG vaccination is common in countries with an intermediate and high TB burden compared with countries with a low TB burden.

The stratified analyses identified heterogeneity between strata for several of these factors but are limited by few studies in some of the strata we evaluated. Factors influencing sensitivity estimates were not consistent among all tests (or induration thresholds for TST), limiting our ability to draw definitive conclusions. For some tests, estimates for sensitivity were higher in countries with a low TB burden compared with countries with an intermediate or high TB

burden. For example, sensitivity of TST at a 10-mm induration threshold was 0.88 (95% CI, 0.76 to 0.99; 3 studies, N=424) compared with 0.72 in countries with an intermediate burden (95% CI, 0.65 to 0.79; 6 studies, N=416) (**Appendix F Figure 13**). We could not identify sources of heterogeneity for sensitivity estimates that were consistently present across the studies of the three IGRA tests.

Specificity of Screening Tests

Similarly, because no direct test for LTBI exists, we relied on 18 primary studies in countries with a low or intermediate TB burden among healthy persons known to be free of TB risks and exposures to estimate specificity.[53,54,69,75,86,93,113-124]

Study Characteristics

Fourteen studies estimated specificity of TST,[53,54,69,75,113-118,120-123] five studies for T-SPOT.TB,[69,75,86,121,123] three studies for QFT-G,[69,118,119] and four studies for QFT-GIT.[86,93,123,124] Characteristics of studies are described in **Appendix D Tables 3** and **4**. All studies were conducted in countries with a Human Development Index of "very high." Three studies were conducted in countries with an intermediate TB burden;[69,75,93] one study was conducted in two countries, one with a low TB burden and the other intermediate;[86] and the remaining 14 studies were conducted in countries with a low TB burden (10 in the United States). Four studies were conducted in populations with more than 75 percent BCG vaccination,[69,75,93,122] nine studies included less than 5 percent BCG-vaccinated participants,[53,54,113,114,117,118,120,121,123] and BCG vaccination was not reported in five studies.[86,116,119,124,125]

Results

We calculated a pooled estimate for specificity of TST at a 10-mm threshold of 0.97 (95% CI, 0.96 to 0.99; I^2=94.3%) and at a 15-mm threshold of 0.99 (95% CI, 0.98 to 0.99; I^2=91.7%). The pooled estimate for specificity of T-SPOT.*TB* was 0.95 (95% CI, 0.92 to 0.98; I^2=79.1%). The pooled estimate for specificity of QFT-G was 0.98 (95% CI, 0.90 to 1.0) and the pooled estimate for QFT-GIT was 0.97 (95% CI, 0.94 to 0.99; I^2=93.4%). The limited number of available studies precluded quantitative synthesis for TST at a 5-mm threshold. Estimates are summarized in **Table 2** and **Figure 5**. The percentage of IGRA tests with indeterminate results ranged from 0 to 3 percent in studies reporting this information.

As part of a sensitivity analysis, we added five studies[94,103,105,108,126] that had been excluded for poor quality and found similar results (**Appendix D Tables 7** and **8**; **Appendix F Figure 3**). We repeated all analyses using a maximum likelihood–based method for random effects and found similar point estimates but with slightly larger CIs (**Appendix F Figure 6**). Because of substantial heterogeneity among studies, we stratified results based on country TB burden and BCG vaccination prevalence (**Appendix F Figures 32–44**). Across all tests, specificity was substantially lower in countries with an intermediate TB burden than in countries with a low TB burden, yet removing these studies had marginal effect on the overall pooled estimates and inconsistency as measured by I^2. For example, at the TST threshold of 10 mm, we removed the one study conducted in a country with an intermediate TB burden that had a specificity of 0.45;

the pooled estimate changed from 0.97 to 0.98 and the I^2 statistic was reduced from 94.3 to 91.2 percent (**Appendix F Table 34**).

Reliability of Screening Tests

We identified nine studies of good or fair quality assessing the reliability of at least one of the included screening tests.[75,113,114,123,127-131]

Study Characteristics

Study characteristics are shown in **Appendix D Table 9**. Three studies assessed the interrater reliability of TST.[113,114,123] Two studies assessed the interrater reliability of T-SPOT.*TB*,[75,128] one assessed the interrater reliability of QFT-GIT,[130] and one assessed the interlaboratory reliability of QFT-GIT.[129] Two studies assessed the test-retest reliability of T-SPOT.*TB* and QFT-GIT 1 to 4 weeks after an initial test.[127,131,132] Eight studies were conducted in countries with a low TB burden (seven in the United States and one in the Netherlands), one study was conducted in a country with an intermediate TB burden[75] (Turkey), and one study enrolled Nepalese military recruits who had left Nepal and recently entered the United Kingdom.[131] Two studies reported the percentage of the study population that had HIV; less than 1 percent in both studies were HIV positive.[127,131] In two studies the majority of participants were BCG vaccinated.[75,131]

Results

Interrater reliability. Three studies (N=1,826,[123] N=1,189,[114] and N=127[113]) measured the interrater reliability of TST results by reporting the kappa statistic for agreement by TST reaction size; results ranged from 0.55 to 0.79, indicating moderate to substantial agreement between two observers. One study (N=91) found substantial agreement between two observers for manually reading T-SPOT.*TB* results (kappa=0.92) and manual versus automatic enzyme-linked immunosorbent spot (ELISpot) readings (kappa=0.73).[75] One study (N=313) evaluated agreement among six individual ELISpot readers; all kappa values were greater than 0.6.[128] One study (N=146) assessed interrater reliability for manual versus automated enzyme-linked immunosorbent assay readings for QFT-GIT; each study participant had two blood draws and each sample was sent for both automated and manual readings.[130] Across all samples, 88.6 percent of results were concordant and 11.0 percent were discordant; the discordance rates for specific comparisons were 4.8 percent (between two different automated readings, kappa=0.85), 6.9 percent (between two different manual readings, kappa=0.80), and 3.4 percent (manual compared with automated readings, kappa ranged from 0.73 to 0.90 across comparisons).[130]

Interlaboratory reliability. One study (N= 91) evaluated the interlaboratory reliability of QFT-GIT by sending three blood specimens from each participant to three different laboratories noted to have extensive experience and proficiency with IGRA testing and interpretation.[129] Across all three laboratories, 7.7 percent of participants had discordant results (none had indeterminate results); kappas of pairwise laboratory sample comparisons ranged from 0.87 to 0.93.[129]

Reproducibility and test-retest reliability. One study (N= 130) assessed the reliability of IGRA results by processing two blood samples from each study participant (using the same

laboratory and same type of test interpretation); 5.8 percent of participants had discordant results for QFT-GIT and 6.5 percent had discordant results for T-SPOT.*TB*.[127] Two studies measured the test-retest reliability of QFT-GIT. One study enrolled U.S. health care workers[127] and one enrolled a population from a country with a high TB burden (Nepal).[131,132] In the study (N=130) enrolling health care workers, 8 percent of baseline T-SPOT.*TB* negative tests changed to positive and 53 percent of positive tests changed to negative on repeat testing at 2 weeks; for QFT-GIT, 8 percent of negative tests changed to positive and 33 percent of positive tests changed to negative.[127] Finally, in the study enrolling a Nepalese population, the kappa statistic for agreement between initial QFT-GIT test and retest at 1 week was 0.48 (95% CI, 0.26 to 0.70) and was 0.66 (95% CI, 0.5 to 0.83) for T-SPOT.*TB*.[131]

KQ 2b. Accuracy and Reliability of Sequential Screening Strategies

We found no eligible studies that addressed this question.

KQ 3. Benefits of Treatment of LTBI

We included three RCTs (Thompson 1982, Menzies 2008, Sterling 2011) assessing treatment of LTBI that met all eligibility criteria (**Appendix D Table 10**).[133-135] One compared isoniazid with placebo,[135] one compared rifampin with isoniazid,[133] and one compared rifapentine plus isoniazid with isoniazid alone.[134]

We identified four additional RCTs (Bush 1965, Falk 1978, Ferebee 1963, Veening 1968) that compared isoniazid with placebo that did not meet all eligibility criteria but were used in sensitivity analyses (**Appendix D Table 13**). For RCTs to be included in sensitivity analyses, we required that they either confirmed LTBI for subjects to be eligible (e.g., by enrolling only those who were tuberculin positive), reported data for subjects with confirmed LTBI (e.g., for the tuberculin-positive subset of subjects), or that the vast majority of subjects (>75%) were tuberculin positive. These trials met many of our eligibility criteria but used a longer duration of treatment than is currently recommended by the CDC[41-44] (i.e., ≥1 year of isoniazid), and some used lower or higher doses than currently recommended[42,43] or did not require LTBI confirmation for subjects to be eligible.[41,43,44] One of the four trials was rated poor quality for high risk of selection bias, attrition bias, confounding, and measurement bias.[42]

Our searches identified additional RCTs that compared isoniazid with placebo, which we excluded from this review. Reasons for excluding studies from this review are listed in **Appendix C**. For example, several trials focused on the use of isoniazid among household contacts of active TB cases but did not require LTBI confirmation for study entry;[136-138] more than half of the participants in these trials were children; trials evaluated 1 year or more of isoniazid treatment; and one trial used a higher dose[138] than is currently recommended by the CDC. Two other trials randomized households or villages to evaluate the prophylactic use of isoniazid in areas with a high prevalence of active TB at the time of the study (Greenland[139] or Alaska[140]). These two trials did not require LTBI confirmation for study entry. One trial evaluated an unusual isoniazid regimen (400 mg for 3 months, nothing for 3 months, then 400 mg for 3 months[139]); the other evaluated 1 year of isoniazid and included many children.[140] Other

excluded RCTs evaluated patients with silicosis[141] or renal transplant and dialysis patients.[142]

Isoniazid Compared With Placebo

The International Union Against Tuberculosis (IUAT) trial was the single trial meeting all eligibility criteria that compared isoniazid with placebo.[135] It randomized 27,830 adults from seven European countries with fibrotic pulmonary lesions but not active TB or previous antituberculosis treatment to four groups: isoniazid 300 mg daily for 12 weeks, isoniazid 300 mg daily for 24 weeks (currently a CDC-approved regimen), isoniazid 300 mg daily for 52 weeks, or placebo. Participants were required to have an induration of 6 mm or larger on TST. The median age was 50 years and 53 percent were men.

After 5 years of followup, 76 (1.1%), 34 (0.5%), 24 (0.3%), and 97 (1.4%) participants developed active TB in the four groups, respectively (**Appendix D Table 11**). The RRs for developing active TB compared with placebo were 0.79 (95% CI, 0.58 to 1.06), 0.35 (95% CI, 0.24 to 0.52), and 0.25 (95% CI, 0.16 to 0.39), respectively (**Figure 6**). For the 24-week CDC approved regimen, we calculated a number needed to treat (NNT) of 112 to prevent 1 case of active TB. Our sensitivity analyses using data from the 24- and 52-week groups from the IUAT trial and four additional RCTs, including a total of 36,823 participants, found an RR of 0.31 (95% CI, 0.24 to 0.41) and no statistical heterogeneity in effects between studies (I^2=0.0%) (**Figure 7**; **Appendix D Table 14**).

The IUAT trial found that persons with larger fibrotic pulmonary lesions had a greater risk of developing active TB. The incidence of active TB in the placebo group was half as great among persons with lesions smaller than 2 cm^2 (11.6 cases per 1,000 population) than among persons with larger lesions (21.3 cases per 1,000 population).

There were no deaths due to TB in any of the isoniazid groups in the IUAT trial; three persons died from TB in the placebo group. The RR for death due to TB was 0.14 (95% CI, 0.01 to 2.78) for each of the isoniazid groups compared with placebo. All-cause mortality was not reported separately for the four groups. The trial reported benefit-to-risk ratios (defined as cumulative TB cases prevented/cumulative hepatitis cases incurred) of 1.2, 2.6, and 2.1 for the isoniazid groups compared with placebo, respectively.

Rifampin Compared With Isoniazid

The one included RCT making this comparison was an open-label trial conducted in Canada, Brazil, and Saudi Arabia that randomized 847 participants to 4 months of rifampin or 9 months of isoniazid to compare adverse events and treatment completion.[133] Because this RCT was focused largely on adverse events, it is described in greater detail with the results for KQ 5. We mention it briefly in this section because it reported zero deaths from TB in either group. It also reported all-cause mortality, with zero deaths in the rifampin group and one in the isoniazid group.

Rifapentine Plus Isoniazid Compared With Isoniazid Alone

The one included RCT making this comparison, the PREVENT TB study, was an open-label, noninferiority trial conducted in the United States, Canada, Brazil, and Spain that randomized 7,731 persons age 12 years or older to directly observed once-weekly rifapentine (900 mg) plus isoniazid (900 mg) for 3 months or to daily self-administered isoniazid (300 mg) for 9 months.[134] The primary endpoint was development of confirmed TB. Subjects were primarily from the United States and Canada (89% of those randomized) and were high-risk persons with a positive TST. Most (71%) had a close contact with a patient with culture-confirmed, active TB within the past 2 years; 25 percent were included solely because of recent conversion to TST positivity. Less than 3 percent of participants were HIV positive; the participants with HIV were not required to have a positive TST. Risk factors for TB included a history of incarceration (5.1%), history of injection drug use (3.7%), and homelessness (27.8%).

Almost 90 percent of subjects randomized completed 33 months of followup. Active TB developed in seven persons in the combination therapy group and in 15 persons in the isoniazid-only group. The combination therapy group was found to be noninferior to the isoniazid-only group. The trial identified 70 deaths from any cause (31 vs. 39 deaths; p=0.22).

From among the 7,731 randomized, we obtained data from the CDC for the subset of participants most directly relevant for this review: the 6,886 adults (age ≥18 years) who were HIV negative and TST or IGRA positive. The median age for this subset was 37 years, 54.2 percent were male, and 57 percent were white. For this subset, active TB developed in five persons in the combination therapy group and in 10 persons in the isoniazid-only group. The combination therapy group was found to be noninferior to the isoniazid-only group. Overall mortality was similar for the two groups (30 vs. 34 deaths, respectively; p=0.42).

KQ 4. Harms of Screening for LTBI

We did not identify any studies addressing this question.

KQ 5. Harms of Treatment of LTBI

We included five RCTs assessing harms associated with the treatment of LTBI that met all eligibility criteria (**Appendix D Table 10**).[133-135,143,144] One compared isoniazid with placebo,[135] three compared rifampin with isoniazid,[133,143,144] and one compared rifapentine plus isoniazid with isoniazid alone.[134]

We identified five additional RCTs that evaluated harms associated with treatment of LTBI that did not meet all eligibility criteria but were used in sensitivity analyses (**Appendix D Table 13**). Criteria for RCTs to be included in sensitivity analyses for KQ 5 are the same as those described for KQ 3. The five additional trials met many of our eligibility criteria, but four of the five trials used a longer duration of treatment than is currently recommended by the CDC[41,43,44,145] (i.e., ≥1 year of isoniazid), one used a shorter duration than is currently recommend by the CDC (3 months of isoniazid),[146] and some used a lower dose than currently recommended[43] or did not

require LTBI confirmation for subjects to be eligible.[41,43,44,145,146] We rated two of these trials as fair quality[145,146] and the other three as poor quality.[41,43,44] Our searches identified additional RCTs and one observational study that compared isoniazid with placebo, which we excluded from this review. Reasons for excluding studies from this review are listed in **Appendix C**.

From this body of evidence, we were able to quantitatively synthesize harms related to hepatotoxicity and discontinuation of medication due to adverse events. Studies also reported a variety of gastrointestinal (GI) adverse events, but we were unable to quantitatively synthesize these outcomes because of heterogeneity in how they were measured across included studies. For example, GI adverse events were reported as a single combined value per treatment arm in one study,[43] as rates of treatment discontinuation due to GI events in another study,[147] and by separate types of GI events (i.e., nausea, clay-colored stools, or anorexia) with no summary rate in a third study.[146] No studies reported harms related to peripheral neuropathy or development of drug-resistant TB.

Isoniazid Compared With Placebo

The IUAT trial was the single trial meeting all eligibility criteria that compared isoniazid with placebo.[135,147] Study characteristics for this trial were previously described (see KQ 3 results); the quality of this study was rated as fair for KQ 5 outcomes because harm outcomes were not prespecified and ascertainment techniques were not adequately described, except for the hepatotoxicity outcomes.

Hepatotoxicity

The IUAT trial reported rates of hepatotoxicity development (**Appendix D Table 12**).[135] The RRs for developing hepatotoxicity associated with isoniazid compared with placebo were 3.45 (95% CI, 1.49 to 7.99) for 12 weeks of treatment, 4.59 (95% CI, 2.03 to 10.39) for 24 weeks of treatment, and 6.21 (95% CI, 2.79 to 13.79) for 52 weeks of treatment (**Figure 8**). For the study arms comparing the 24-week CDC-approved regimen with placebo (N=13,955), we calculated that 1 case of hepatotoxicity would result from treating 279 persons with isoniazid (i.e., a number needed to harm [NNH] of 279). Our sensitivity analyses using data from the IUAT trial (three treatment arms combined) and three additional RCTs,[41,145,146] including a total of 35,161 participants, found an RR of 5.04 (95% CI, 2.50 to 10.15) and no statistical heterogeneity among studies (I^2=0.0%; p=0.630) (**Appendix G Figure 1**).

The one RCT included in the main analysis comparing isoniazid with placebo for treatment of LTBI[135] reported mortality rates from hepatotoxicity of 0.03 percent, 0.0 percent, and 0.01 percent for the 12-, 24-, and 52-week isoniazid treatment groups, respectively. This study had zero deaths from hepatotoxicity among placebo-treated patients. The authors reported that the mortality rate from hepatitis associated with isoniazid was 0.14 deaths per 1,000 persons receiving isoniazid, for a calculated RR of 2.35 (95% CI, 0.12 to 45.46; NNH, 6,947).

Treatment Discontinuation Because of Adverse Events

Rates of treatment discontinuation because of adverse events in the IUAT trial were presented

only for all three isoniazid treatment groups combined. A total of 345 patients (1.8%) receiving isoniazid discontinued treatment because of adverse events compared with 84 patients (1.2%) receiving placebo. The RR of discontinuation due to adverse events among patients treated with isoniazid versus placebo was 1.50 (95% CI, 1.18 to 1.89; 1 RCT, N=27,830; NNH, 167). Our sensitivity analysis using data from the IUAT trial and three additional RCTs,[43,44,146] including a total of 55,398 participants, found an RR of 1.58 (95% CI, 1.00 to 2.49; I^2=70.2) (**Appendix G Figure 2**).

GI Adverse Events

The IUAT trial reported that 1.2 percent of isoniazid patients and 0.9 percent of placebo patients discontinued treatment due to GI distress.[147] The RR of discontinuation due to GI distress among isoniazid versus placebo patients was 1.33 (95% CI, 1.01 to 1.75). Among studies included in sensitivity analyses, one[43] reported GI adverse events (0.7% in isoniazid group vs. 0.3% in placebo group) and one[146] reported nausea (3.3% in isoniazid group vs. 1.7% in placebo group), clay-colored stools (10.0% in isoniazid group vs. 5.0% in placebo group), and anorexia (8.3% in both isoniazid and placebo groups).

Other Harms

No other adverse events were reported in the IUAT trial.[135] A variety of other adverse events were reported in the RCTs included in sensitivity analyses. Rates of other adverse events were generally similar among isoniazid and placebo patients (**Appendix D Table 15**). One study reported an increased risk for rash (0.9% of isoniazid patients and 0.3% of placebo patients; RR, 2.7 [95% CI, 1.27 to 5.73]).[41,148]

Rifampin Compared With Isoniazid

Three open-label RCTs compared rifampin with isoniazid (**Appendix D Table 10**). One trial conducted in Canada (N=116) compared 4 months of rifampin (10 mg/kg of body weight, up to 600 mg/day) with 9 months of isoniazid (5 mg/kg, up to 300 mg/day).[143] Participants were age 18 years or older with documented LTBI; more than half were male. A later study by the same authors conducted in Canada, Brazil, and Saudi Arabia randomized 847 participants to the same two treatments.[133] Participants were age 18 years or older with documented LTBI; just over half were male. The third trial randomized inmates (N=365) in the San Francisco City and County Jail diagnosed with LTBI at jail entry to 9 months of isoniazid (900 mg twice per week) or 4 months of rifampin (600 mg/day).[144] Ninety-three percent of study participants were male.

Hepatotoxicity

Rates of hepatotoxicity in these three RCTs among patients receiving isoniazid were 5.2 percent,[143] 3.7 percent,[133] and 11.4 percent[144] (**Appendix D Table 12**). Rates among rifampin-treated patients were 0.0 percent, 0.7 percent, and 4.4 percent, respectively. The RRs of hepatotoxicity from these three RCTs of isoniazid compared with rifampin were 7.00 (95% CI, 0.37 to 132.56), 5.25 (95% CI, 1.54 to 17.87), and 2.57 (95% CI, 1.17 to 5.65), respectively. Our meta-analysis of these three RCTs (total N=1,327) found a greater risk of hepatotoxicity for

patients treated with isoniazid than for those treated with rifampin (RR, 3.29 [95% CI, 1.72 to 6.28]; I^2=0.0%) (**Figure 9**). All studies reported zero deaths from hepatotoxicity.

Treatment Discontinuation Because of Adverse Events

Rates of discontinuation because of adverse events were reported in all three included RCTs. Rates were 13.8 percent (isoniazid) and 3.4 percent (rifampin);[143] 5.6 percent (isoniazid) and 3.8 percent (rifampin);[133] and 0.0 percent (isoniazid) and 1.1 percent (rifampin)[144] (**Appendix D Table 12**). The RR of discontinuation due to adverse events for isoniazid compared with rifampin for these three studies was 4.0 (95% CI, 0.89 to 18.04), 1.48 (95% CI, 0.80 to 2.74), and 0.20 (95% CI, 0.01 to 4.05), respectively. Our meta-analysis found no statistically significant difference between treatments (RR, 1.61 [95% CI, 0.57 to 4.57]; I^2=40.0%; N=1,327) (**Figure 10**).

GI Adverse Events

Among the three included RCTs, one reported GI adverse events in 3.4 percent of the study population, not separated by treatment arm.[143] One reported grade 1/2 GI intolerance among 0.2 percent of rifampin patients and 0.5 percent of isoniazid patients.[133] The third study reported GI adverse events among 9 percent of rifampin patients and 10 percent of isoniazid patients.[144] The pooled RR among the two studies reporting adverse events by treatment arm was 1.60 (95% CI, 0.76 to 3.40; I^2=0%; N=1,211).

Other Harms

The three RCTs in the main analysis reported on various other harms (**Appendix D Table 12**). None of these harms involved statistically significant differences in RR for isoniazid compared with rifampin. The pooled RR for adverse events categorized as "other" by two RCTs was 0.82 (95% CI, 0.42 to 1.59; 3 RCTs; I^2=0%; N=480).[143,144]

Rifapentine Plus Isoniazid Compared With Isoniazid

The one included RCT making this comparison, the PREVENT TB study, was an open-label, noninferiority trial conducted in the United States, Canada, Brazil, and Spain that randomized 7,731 persons age 12 years or older to directly observed once-weekly rifapentine at 900 mg plus isoniazid at 900 mg for 3 months, or to daily self-administered isoniazid at 300 mg for 9 months.[134] More details regarding this study are presented in the results section on benefits of treatment (KQ 3).

Hepatotoxicity

Rates of grade 3 and 4 hepatotoxicity were 4.9 and 1.0 percent in the rifapentine plus isoniazid arm and 5.5 and 1.1 percent in the isoniazid-only arm, respectively. The RR for grade 3 or 4 hepatotoxicity was 0.90 (95% CI, 0.75 to 1.08). Mortality from hepatotoxicity was reported in 1.0 percent of isoniazid patients and 0.8 percent of isoniazid plus rifapentine patients (RR, 0.83 [95% CI, 0.51 to 1.35]).

Treatment Discontinuation Because of Adverse Events

Rates of discontinuation because of adverse events were 5.2 percent in the rifapentine plus isoniazid arm and 4.1 percent in the isoniazid-only arm. The RR of treatment discontinuation due to adverse events for the rifapentine plus isoniazid versus isoniazid-only arm was 1.28 (95% CI, 1.03 to 1.59).

Other Harms

Possible hypersensitivity was reported in 0.5 percent of isoniazid patients and 4.1 percent of isoniazid plus rifapentine patients. The RR of possible hypersensitivity for rifapentine plus isoniazid versus isoniazid-only patients was 8.04 (95% CI, 4.88 to 13.26).

Chapter 4. Discussion

Summary of Evidence

Tables 3–5 provide a summary of findings in this evidence review. These tables, which are presented by KQ, provide a summary of outcomes organized by test or intervention along with a description of precision, risk of bias, and applicability.

Evidence for Benefit and Harms of Screening

We did not identify any RCTs or prospective cohort studies directly assessing the effectiveness or harms of screening for LTBI compared with no screening in the populations and outcomes specified for this review.

Accuracy and Reliability of Screening Tests

The evidence on accuracy and reliability was based on fair-quality evidence overall. Because of the lack of tests for the direct diagnosis of LTBI, evaluating accuracy of tests relies on extrapolation from test characteristics among populations with active, confirmed TB (sensitivity) or from healthy persons known to be free of TB risks and exposures (specificity). The evidence suggests that for the populations studied, currently available tests are moderately sensitive and, in countries with a low TB burden, highly specific. Sensitivity estimates for TST (at 5-mm and 10-mm but not 15-mm thresholds) and QFT IGRAs were consistent, with pooled estimates ranging from 0.77 to 0.80. Sensitivity estimates for the T-SPOT.*TB* IGRA test were higher at 0.90, and estimates of sensitivity for IGRA tests were more precise than those for TST. Pooled estimates for specificity of TST at 10- and 15-mm thresholds and all IGRA tests ranged from 0.95 to 0.99. We judged specificity estimates to be consistent and precise in countries with a low TB burden. Our findings for sensitivity and specificity are generally consistent with other systematic reviews evaluating accuracy, despite differences in study inclusion and exclusion criteria.[149-152] We found limited evidence on the reliability of these tests and, of those identified, few assessed reliability in the same way.

The applicability of the evidence on accuracy and reliability of screening tests to primary care practice settings and populations is uncertain, since the lack of a direct test for LTBI requires test accuracy studies to be performed in specific populations (e.g., populations with active, confirmed TB; healthy, low-risk populations) to ensure the validity of findings. We found lower estimates for specificity in studies conducted in populations from countries with an intermediate TB burden. This could be the result of unintentional inclusion of subjects with unknown past TB exposure, thus increasing the frequency of positive results; inclusion of BCG-vaccinated subjects; thus increasing false-positive TST results; or because of other factors that affect the administration or interpretation of tests among populations in these countries.

Despite this uncertainty, the evidence is likely applicable to primary care practice settings that serve high-risk populations (e.g., public health settings, residents of high-risk congregate

settings, clinics serving foreign-born populations), where the use of a highly specific test among a higher prevalence population minimizes false positives and results from a moderately sensitive test can be combined with a clinical risk assessment to determine the likelihood of infection to inform treatment decisions. In these settings, clinical risk assessment prior to testing may already be a part of standard clinical workflow, and clinic and laboratory staff may have extensive experience with appropriate testing techniques and interpretation. However, many primary care practice settings may not serve large populations at high risk for LTBI; thus, an approach that relies on an individualized clinical assessment for LTBI risk to inform decisions regarding testing may not be part of standard workflow. Systematic identification of high-risk persons cared for in low-prevalence practice settings may be challenging and associated with opportunity costs.

Benefits and Harms of Treatment of LTBI

The best evidence on effectiveness of treatment of LTBI with a CDC-recommended regimen was from the IUAT trial, a large (N=27,830) good-quality study. It found a 65 percent relative reduction in progression to active TB at 5 years for 24 weeks of isoniazid compared with placebo (NNT, 112). Our sensitivity analysis adding four RCTs (that did not meet all of our eligibility criteria) that used a longer duration of treatment and some different doses than currently recommended found a similar reduction. The IUAT trial enrolled subjects with pulmonary fibrotic lesions, a group thought to be at the highest risk for progression to active TB. In this trial, subjects with smaller lesions progressed to active TB at lower rates than those with larger lesions. Further, the populations included in the other treatment studies used in our sensitivity analysis were not persons identified to have LTBI via screening in primary care settings; rather, they were household contacts of active cases,[43] veterans with inactive pulmonary TB,[41,148] persons residing in mental institutions,[44] and military members exposed to an active TB case.[42] Thus, the available evidence may not be applicable to persons in primary care settings who screen positive on TST or IGRA but have normal chest x-rays or who are not recent converters or close contacts. Thus, estimates of treatment effectiveness may represent the upper bounds of effectiveness, which may be lower in other screen-positive populations. Further, all of the RCTs that assessed the effectiveness of isoniazid compared with placebo were published more than 30 years ago (1963, 1965, 1968, 1978, and 1982). Most of them evaluated 1 year of treatment with isoniazid because that was the recommended treatment for many years; shorter durations and other regimens were later studied with a focus on reducing harms (and little attention to evidence on benefits). It is unclear whether changes in the prevalence of TB, treatments for active TB, or likelihood of LTBI progressing to active TB would significantly change estimates of effectiveness.

We found limited evidence on efficacy of other CDC-recommended regimens meeting our eligibility criteria and scant evidence on effectiveness of treatments for reducing mortality due to TB or all-cause mortality. No studies compared rifampin or rifapentine plus isoniazid with placebo or compared a 9-month course of isoniazid with placebo. However, the included head-to-head. open-label, noninferiority RCT (the PREVENT TB trial) that compared a combination of once-weekly rifapentine plus isoniazid for 3 months with daily isoniazid for 9 months found the combination therapy to be noninferior (with estimates trending in favor of combination therapy) to isoniazid alone for preventing the development of active TB.

The evidence on harms was of fair quality overall and suggests a 4.6-fold increased risk for hepatotoxicity for treatment with 6 months of isoniazid compared with placebo and a 3.6-fold increased risk compared with rifampin. Deaths due to hepatotoxicity were rare across all studies included such that estimates were imprecise. In the IUAT trial, all three subjects who died from hepatitis had continued to take isoniazid after liver abnormalities were recognized.[135] Two studies used in sensitivity analysis for harms reported normalization of liver enzyme levels among subjects experiencing asymptomatic elevation[145] or mild hepatitis.[41,148] Discontinuation of treatment because of adverse events was modestly increased for isoniazid compared with placebo, but estimates of no difference between isoniazid and rifampin were inconsistent and imprecise. GI distress, an outcome that represents a heterogeneous group of harms in both type and severity, was inconsistently reported by included studies. Other harms reported were limited by inconsistent and imprecise findings. Other adverse events occurred infrequently and may be subject to more bias in determination than hepatotoxicity or discontinuation because of adverse events.

The overall benefits and harms of screening and treatment are influenced by several factors. The NNT is driven both by the effectiveness of treatment compared with no treatment and by the rate of progression to active TB among an untreated group. Given that treatment of LTBI has been the standard of care for decades, contemporary data for estimating efficacy/effectiveness are not available. A recent study to estimate the cost-effectiveness of screening for LTBI using TST and IGRA among different risk groups specified in current CDC screening guidelines reported similar difficulties in establishing robust estimates of TB reactivation and uncertainty in test characteristics as a result of the lack of a referent standard for diagnosis of LTBI.[153] Proponents for screening suggest benefits on outcomes related to TB transmission and through case-finding of active TB that occurs during screening. However, we identified no studies meeting our study selection criteria that reported on outcomes related to TB transmission.

Hypothetical Outcomes of a Screening Program

The hypothetical outcomes of a screening program for LTBI are illustrated in **Table 6**. These outcomes are a crude approach to estimating the overall benefits and harms of screening in a population, and several scenarios are illustrated to provide alternative outcomes based on differing prevalence of infection and differing rates of progression from latent to active TB. A detailed list of assumptions and relevant citations for assumptions are provided in the table notes.

We calculated outcomes for two different prevalence estimates for LTBI (20.5% for the foreign-born U.S. population and 4.7% for the overall U.S. population) and provided the range of outcomes based on the lower and upper CIs associated with these prevalence estimates (shown in brackets in **Table 6**). For the sensitivity and specificity of tests, we use the pooled estimates from our meta-analysis for TST at the 10-mm threshold, although in practice, the threshold used is typically individualized to the risk of the person being screened. We assumed all persons who test positive receive a chest x-ray to rule out active disease and that a proportion of persons will not be offered treatment based on a history of prior treatment of LTBI or active TB disease. We assumed rates of progression in the absence of treatment based on rates of progression in the placebo arm of the IUAT trial (1.4% at 5 years) and an alternative rate of progression based on more recent estimates (0.084 cases per 100 person-years for overall population and 0.098 cases

per 100 person-years for foreign-born U.S. population).[8] We used an estimate for the RR reduction in progression to active TB for treatment with 6 months of isoniazid based on the IUAT trial (0.35). We assumed rates of hepatotoxicity and discontinuation due to adverse events based on estimates calculated for this review.

For the base case using the foreign-born U.S. population prevalence estimate and rate of progression from the IUAT trial, we estimated that for 100,000 asymptomatic patients screened and eligible for treatment, 18,580 will have a positive test, require a chest x-ray, and be offered treatment. Of these, 2,385 patients will have false-positive tests that do not have any potential to benefit from treatment. Of those treated, 79 patients will progress to active TB despite treatment compared with 225 patients if no screening and subsequent treatment were offered. This is equivalent to an NNT of 111. Under an alternative assumption regarding rate of progression to active TB, we estimated that fewer cases will progress to active TB with (28) or without (79) treatment, and the NNT increases to 314. We had insufficient evidence to estimate benefits relating to prevention of TB deaths, prevention of TB transmission, and improvements in quality of life.

With respect to harms, 85 patients treated with isoniazid for 6 months will experience hepatotoxicity compared with 19 patients if no screening and subsequent treatment were offered, for an NNH of 279. Likewise, 334 subjects would discontinue isoniazid treatment due to adverse events compared with 223 subjects if no screening and treatment were offered, for an NNH of 167. Fewer cases of hepatotoxicity would occur with treatment with rifampin (26) compared with no treatment (19), for an NNH of 2,531. We had insufficient data to estimate outcomes for other types of harms, such as psychological harms, peripheral neuropathy, hematologic reactions, and dermatologic or hypersensitivity reactions.

Overall, the estimated number of active TB cases prevented ranges from 52 to 146, depending on which assumption for progression to active TB is used. Sixty-seven cases of hepatotoxicity would be caused if treatment with isoniazid is used; nine of those cases would be caused by unnecessary treatment in persons with false-positive screening results and no potential to benefit from treatment. One hundred and eleven cases of treatment discontinuation due to adverse events would occur; 14 of those would occur in persons with no potential to benefit (false positives).

Table 6 shows hypothetical outcomes using estimates of LTBI prevalence for the overall U.S. community-dwelling population, a lower prevalence population than the U.S. foreign-born population. For this population, fewer absolute numbers of persons would screen positive and be subjected to treatment and thus experience treatment-related harms. However, more than 40 percent (2,859) of subjects offered treatment (6,572) would have false-positive tests and no potential for benefit yet be subjected to the risk of harms from treatment.

Limitations of the Review

This review is limited in its ability to directly assess the effectiveness of targeted screening for LTBI because we identified no studies comparing screened against unscreened populations among the populations considered in this review. LTBI screening and treatment among some

high-risk persons is a standard of practice. Thus, trials comparing screening with no screening in these populations have not been conducted.

We could not assess screening test characteristics specifically for LTBI because of the absence of a reference standard for direct diagnosis. We relied on extrapolation from studies in active TB populations for sensitivity and in healthy subjects for specificity, an approach consistent with other studies estimating sensitivity and specificity of these tests. We identified a substantial amount of statistical heterogeneity in some of our pooled estimates, although we believe this heterogeneity is not clinically meaningful, and we suspect inflation of I^2 (the proportion of variation in study estimates due to heterogeneity) among specificity outcomes because of very precise individual study estimates.[49] When possible, we stratified analyses by study features possibly contributing to the heterogeneity, but few studies were available for some of the strata used in analysis, and with rare exceptions, findings were not consistent for explaining heterogeneity across tests (or induration thresholds for TST). We did not stratify findings by reagent used for TST (PPD vs. RT-23); the equivalence between these two reagents has not been established in recent years and may have contributed to heterogeneity in findings.

The studies of screening tests in our review did not consistently report comorbidities of the study population tested. Although we excluded studies and results from populations with more than 25 percent HIV-infected persons, patients with active TB often have underlying comorbidities related to immunosuppression, and the extent to which sensitivity of tests is blunted by this underlying immunosuppression is not known and may result in lower estimates of sensitivity than would otherwise be found in populations with latent infection. On the other hand, the presence of active disease may result in more host sensitization than would occur compared with latent infection, such that this population may overestimate the true sensitivity of the tests for latent infection. We did not identify any eligible studies evaluating the sequential use of tests; studies that used more than one test typically performed both tests on the study population to assess concordance rates or used a second test only in the case of an indeterminate or unexpected result on the first test.

Evidence on reliability of tests was limited. For the T-SPOT.*TB* test, manual versus automated reading of specimens could affect reliability, but few studies using T-SPOT.*TB* formally evaluated this. Further, test-retest reliability may vary by baseline prevalence of LTBI; the U.S. study assessing this outcome had a higher rate of reversion from positive to negative compared with the study conducted among Nepalese immigrants. For TST, test-retest reliability is challenging to measure because repeat testing in patients with a positive test is not clinically recommended because of the risk of stimulating an even larger hypersensitivity reaction. Moreover, interpretation of repeat testing among subjects initially testing negative is complicated by the well-known booster phenomenon. Studies of reliability included in this review were not conducted in primary care settings. Both tests (TST and IGRA) have fairly detailed test procedures for administration, handling, and interpretation. The one study assessing IGRA interlaboratory reliability sent specimens to laboratories that have extensive expertise and experience with IGRA testing and interpretation. Thus, the applicability of reliability evidence to primary care practice settings or laboratories that may not have the expertise or economies of scale to perform tests with high fidelity to recommended instructions for testing is uncertain.

We identified no studies assessing the harms of screening compared with no screening. Potential harms include overdiagnosis and treatment of LTBI that would have never progressed to active TB. Potential harms also include incidental findings on chest x-ray in persons who screen positive for LTBI, which result in the need for followup computed tomography scans or serial x-rays for findings unrelated to TB disease, such as lung nodules. This review was also limited in its ability to determine the burden of repeat testing required for persons who have indeterminate results on IGRAs. Last, we did not identify any evidence about psychosocial harms in persons who screen positive and may experience anxiety or stigma associated with being labeled as infected with TB.

This review was limited to the evaluation of existing CDC-recommended LTBI treatment regimens. Isoniazid was established as an effective treatment of LTBI several decades ago; the IUAT trial and the RCTs in our sensitivity analysis were published more than 30 years ago. CDC-recommended treatments have evolved based on interval studies comparing shorter durations and alternative regimens against the standard isoniazid regimen to reduce harms, improve adherence, or both, rather than to assess efficacy. Since the original isoniazid trials were conducted, the prevalence of TB has declined, yet the prevalence of resistant strains among those infected has increased; thus, the applicability of evidence from an era before multidrug TB resistance is unclear. We identified little information on the rate of progression from LTBI to active TB in the modern era, which is an important determinant for making decisions about treatment.

Our review excluded treatments that are not recommended by the CDC and also excluded several populations (e.g., children, persons with HIV). A recent network meta-analysis of treatment of LTBI that used a mixed-treatment comparison methodology suggests that some of the more recently recommended regimens are efficacious for preventing active TB (e.g., rifampin for 3 to 4 months, rifapentine-isoniazid combination), potentially more so than isoniazid alone, and may have fewer adverse effects.[154] This analysis included studies among children; HIV-infected persons; household or close contacts of persons with active TB without confirmed LTBI; and persons with renal transplant, silicosis, or rheumatoid arthritis who are taking immunosuppressive biologic medication, which were all populations excluded from the present review. The meta-analysis also included treatment regimens not eligible for our review. A systematic review conducted for the Cochrane Collaboration on isoniazid for the prevention of TB in non–HIV-infected persons found a significant reduction in active TB over 2 years or longer using data from 11 RCTs (RR, 0.40 [95% CI, 0.31 to 0.52]). The review included studies among children, household or close contacts of active TB patients in the absence of confirmed LTBI, persons with renal transplant, and persons with silicosis, which were all populations excluded from the present review.[155]

Future Research Needs

Continuing declines in TB incidence in the United States during the past several decades suggest progress toward reaching the public health goal of TB elimination. Most active TB cases are reactivations of latent TB rather than new transmission. Risk for LTBI and progression to active TB is on a continuum, and although there is certainty about persons and populations at the

absolute highest risk, there is uncertainty about LTBI prevalence and rates of progression in persons and populations at increased risk but perhaps not the highest absolute risk, such as persons with diabetes and smokers. More research to elucidate the epidemiology of LTBI in these groups could inform future screening and treatment strategies to better tailor individual screening and treatment recommendations. Future research to develop more accurate screening tests, more effective LTBI treatments with fewer harms and side effects, and treatments requiring shorter duration with higher rates of patient adherence would also improve the overall benefit of an LTBI screening program.

In addition to research to improve the accuracy of screening tests and the effectiveness or safety of treatment, research is needed to determine efficient ways of identifying candidates for LTBI testing that take advantage of varied data sources and alternative venues for risk assessment beyond primary care office settings. Primary care settings serving the general population are different from primary care provided in specialized clinics that care for high-risk populations (e.g., prison clinics, clinics serving large proportions of foreign-born populations) and TB-specific public health settings; thus, an approach to clinical risk assessment and testing that can be tailored based on setting and practice characteristics is needed. For example, operations research may be needed to identify efficient ways of identifying high-risk persons who are seen in low-prevalence community practice settings. Further, research that informs our understanding of the incremental net benefit of more or less frequent screening could also help determine optimal approaches to screening.

Conclusion

We identified no studies that directly evaluated the benefits and harms of a screening program for LTBI compared with no screening among the populations considered in this review. Both types of currently available screening tests for LTBI (TST and IGRA) are moderately sensitive and, within countries with a low TB burden, are highly specific. Isoniazid treatment reduces the risk of progression to active TB in persons with LTBI and pulmonary fibrotic lesions. The evidence on benefit on other outcomes (e.g., TB mortality, all-cause mortality) or other treatment regimens is limited or not available for the populations considered in this review. Isoniazid is associated with higher rates of hepatotoxicity than placebo and rifampin regimens. Isoniazid is also associated with higher risk for discontinuation of treatment due to adverse events than placebo, but this risk was similar to the risk for rifampin regimens.

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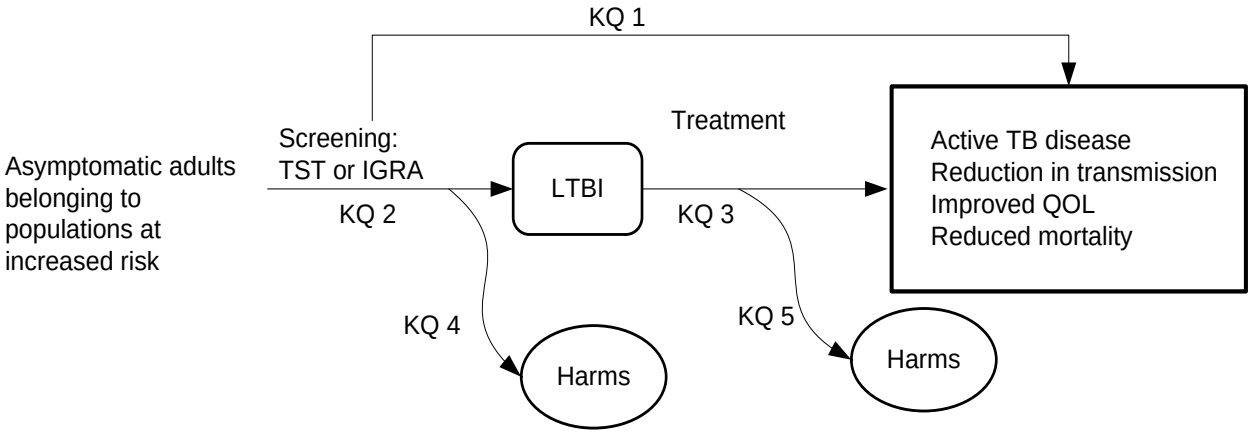
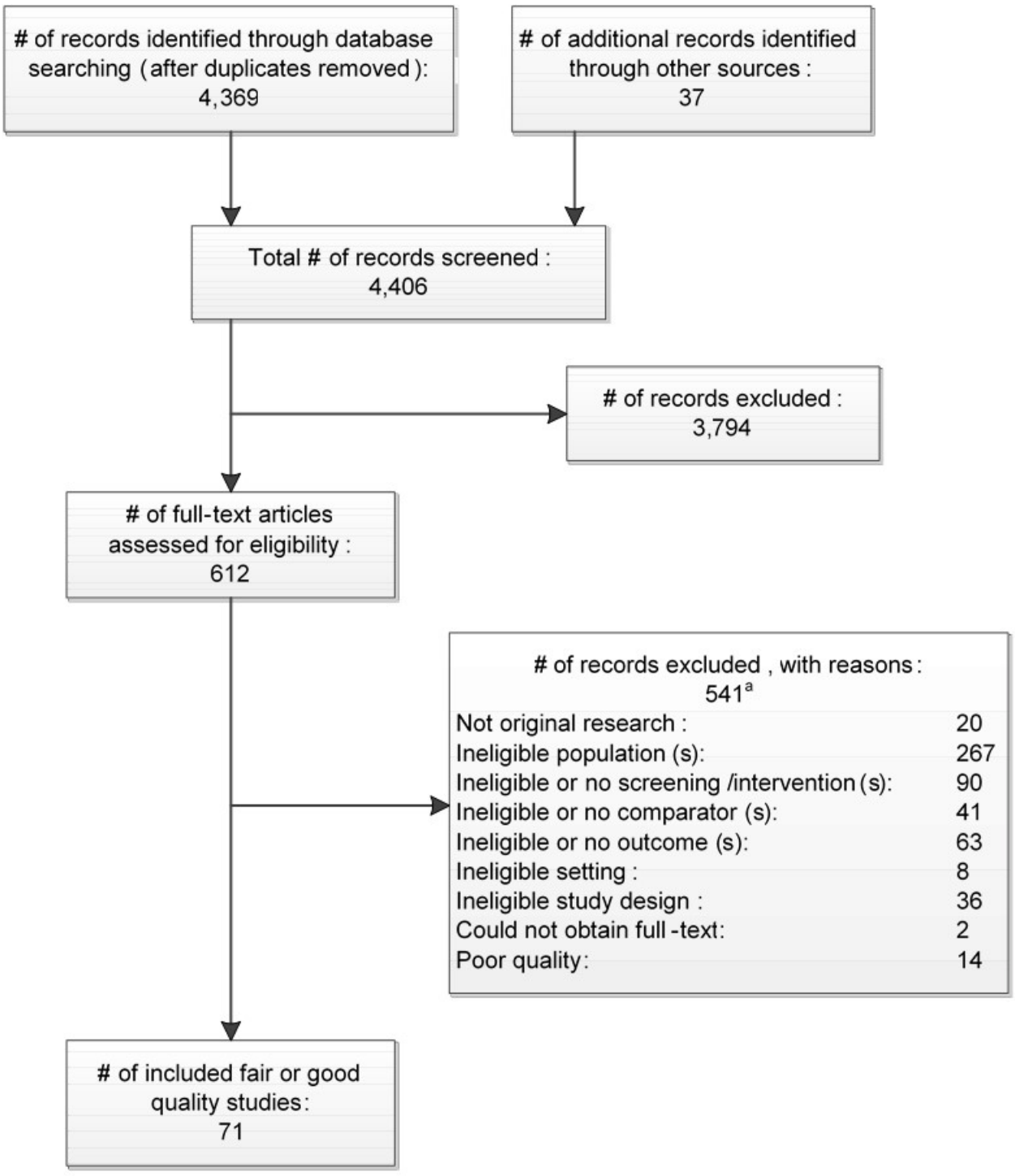
Figure 1. Analytic Framework: Screening for Latent Tuberculosis Infection in Adults



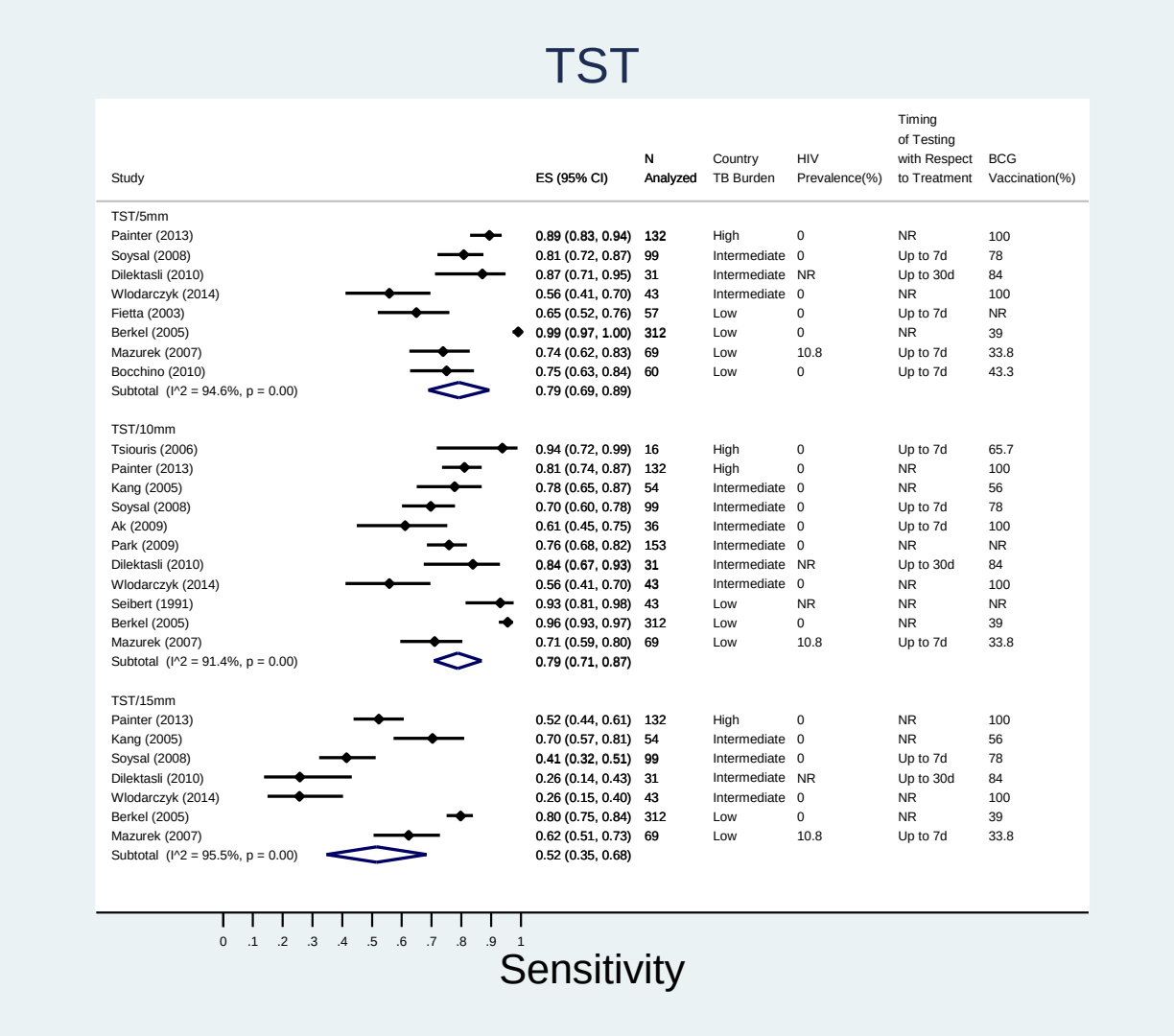
Abbreviations: IGRA=interferon-gamma release assay; KQ=key question; LTBI=latent tuberculosis infection; QOL=quality of life; TB=tuberculosis; TST=tuberculin skin test.

Figure 2. Preferred Reporting of Systematic Review and Meta-Analysis (PRISMA) Tree



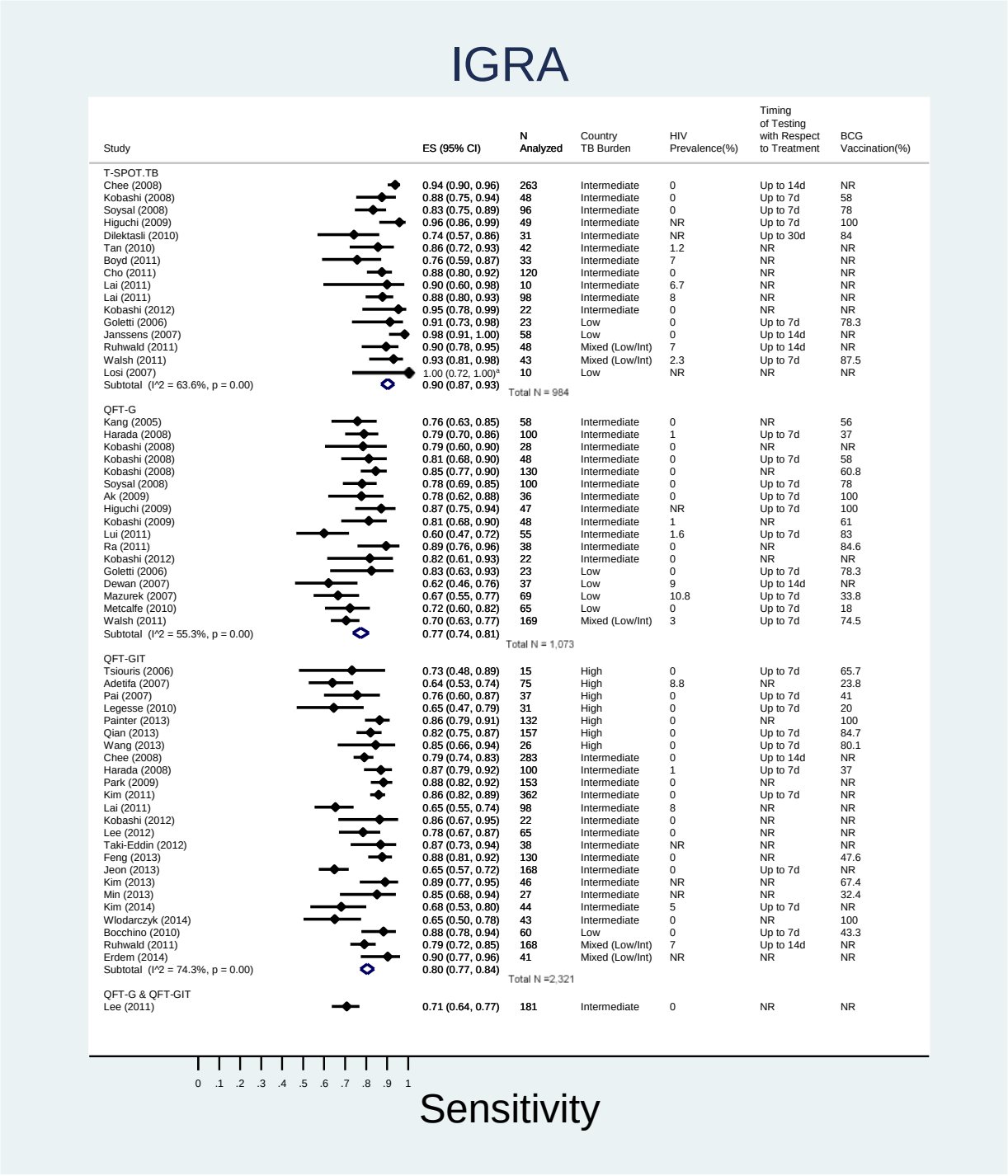
[a] 19 poor-quality and/or ineligible studies were excluded but used in sensitivity analyses.

Figure 3. Individual Study and Pooled Estimates of Sensitivity for Various Thresholds of the Tuberculin Skin Test for Tuberculosis Infection



Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

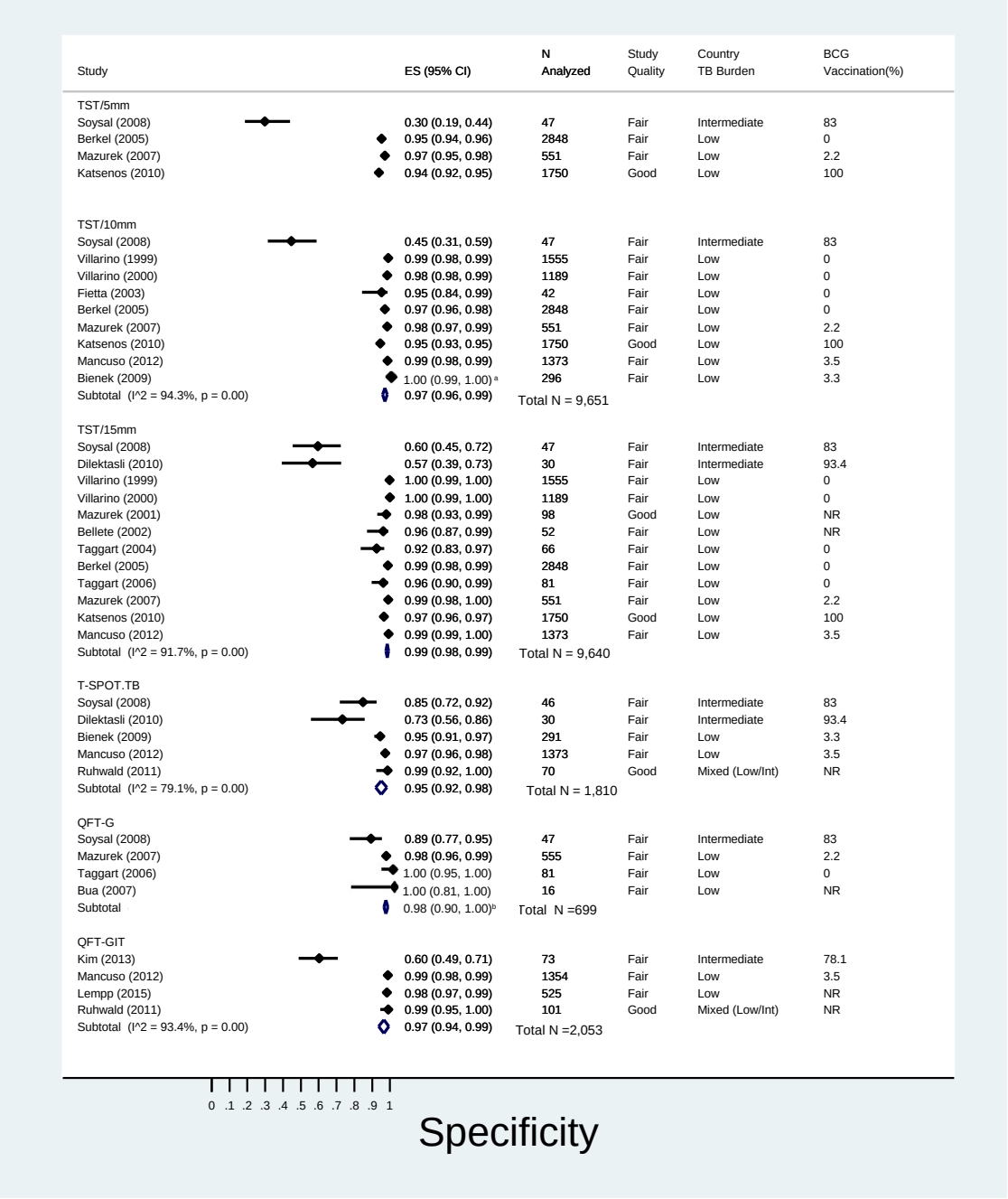
Figure 4. Individual Study and Pooled Estimates of Sensitivity for Interferon-Gamma Release Assay Tests for Tuberculosis Infection



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; Int=intermediate; N=number; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd- generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd-generation test); TB=tuberculosis.

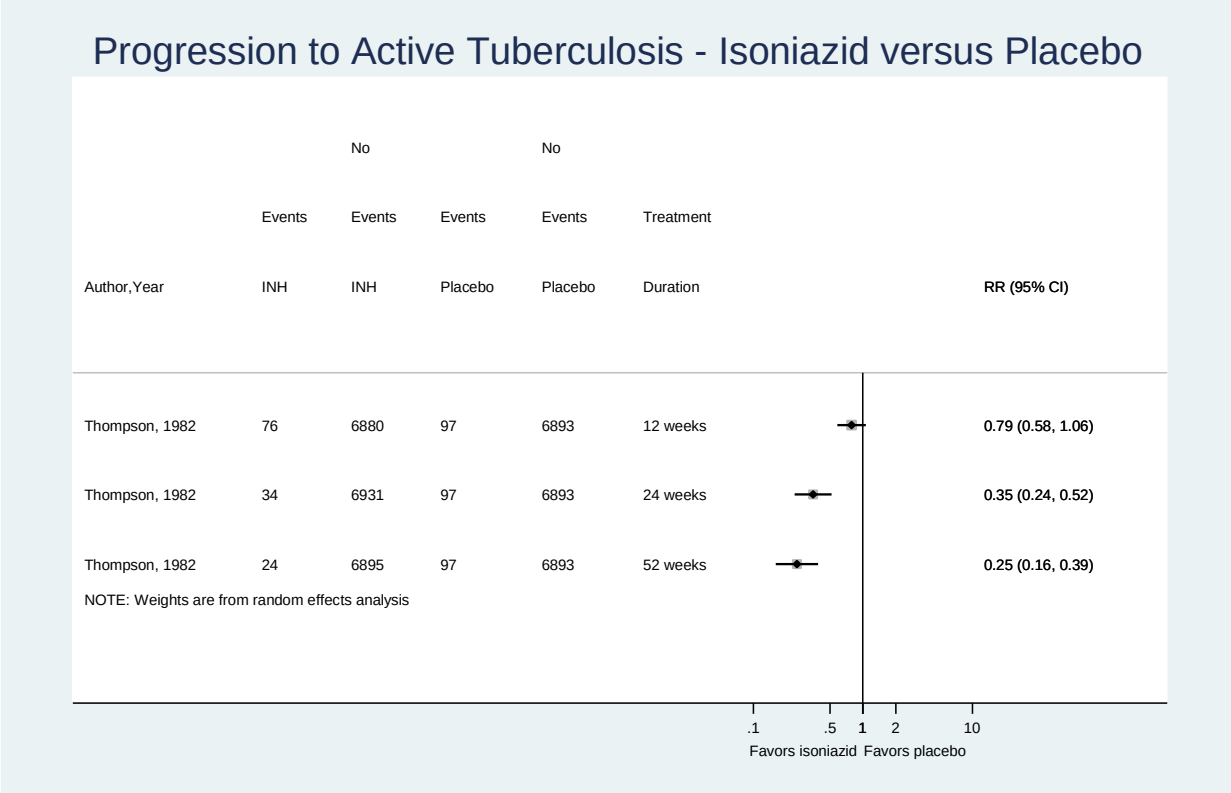
Figure 5. Individual Study and Pooled Estimates of Specificity for Various Thresholds of the Tuberculin Skin Test and Interferon-Gamma Release Assay Tests for Tuberculosis Infection



[a] Excluded from pooled estimate due to point estimate of 1.0.
[b] Pooled estimate from maximum-likelihood estimate random-effects model because of two studies with point estimates of 1.0. No I^2 statistic is calculated using this model.

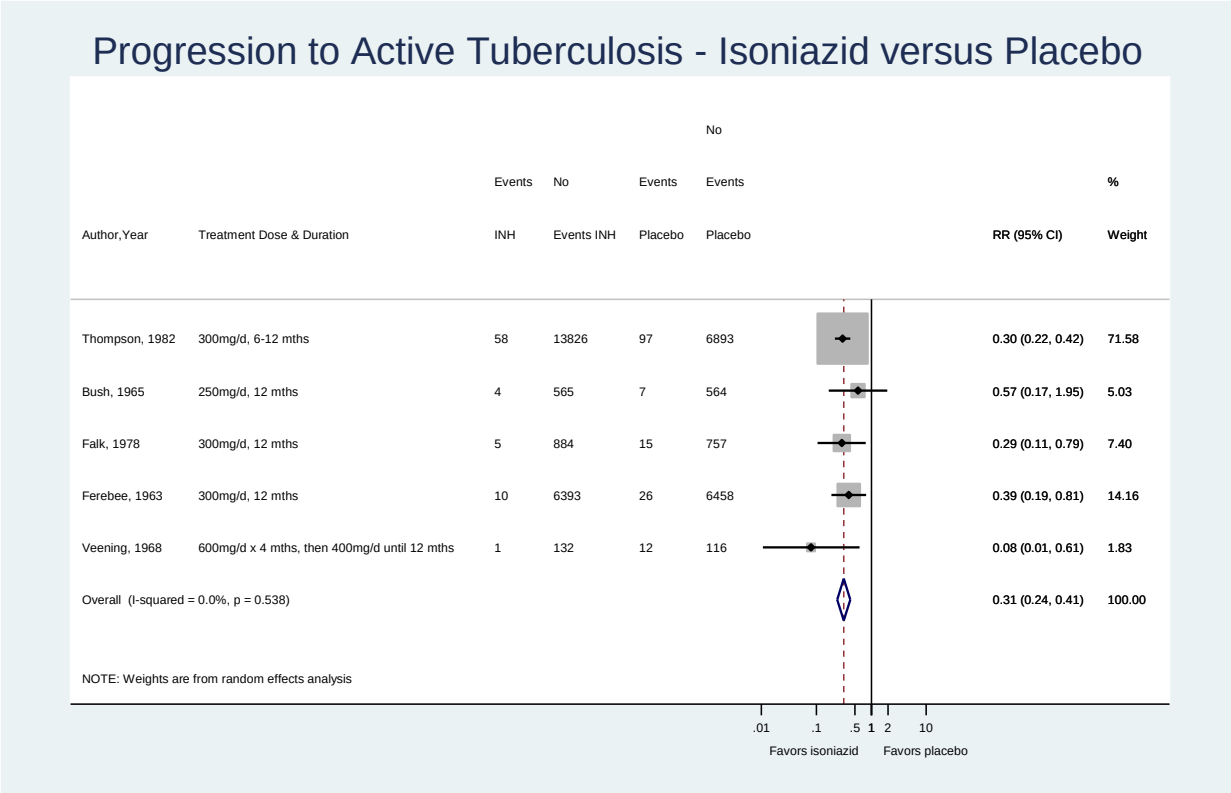
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; Int=intermediate; N=number; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd-generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd-generation test); TB=tuberculosis; TST=tuberculin skin test.

Figure 6. Isoniazid Compared With Placebo: Relative Risk of Developing Active Tuberculosis in the IUAT Trial



Abbreviations: CI=confidence interval; INH=isoniazid; IUAT=International Union Against Tuberculosis; RR=relative risk.

Figure 7. Isoniazid Compared With Placebo: Relative Risk of Developing Active Tuberculosis, Sensitivity Analysis Including Data From the IUAT Trial and Four Additional Randomized, Controlled Trials

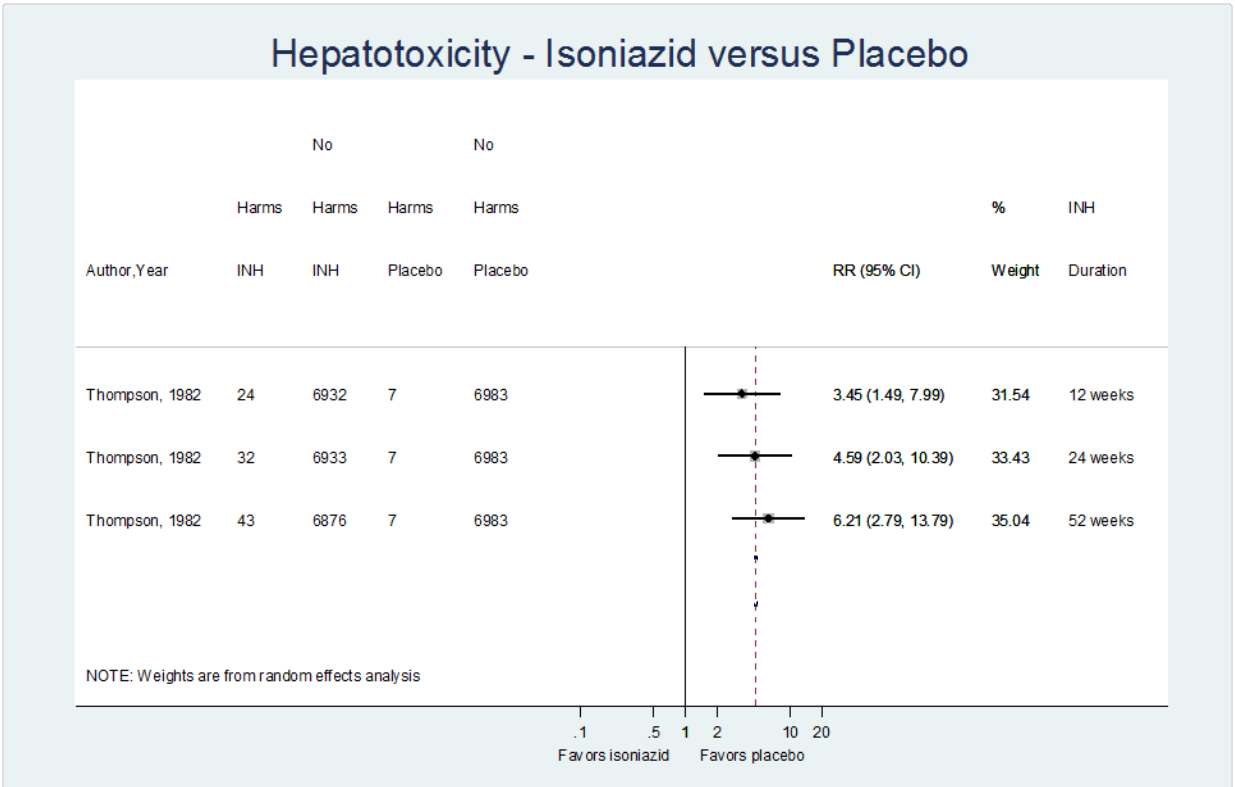


Notes: For Thompson 1982[135] (IUAT trial), we included data from the 24- and 52-week groups. For Bush 1965,[43] we only used data for participants age ≥20 years. For Falk 1978,[41] we used data for the subset with no previous tuberculosis therapy for participants in the isoniazid 1-year group (we did not include data for the isoniazid 2-year group). For Ferebee 1963,[44] we used only the subset that was tuberculin positive; we were unable to get adult-only data to enter here (for the full study sample, 34 of the 51 cases in the placebo arm were among adults, and it was not reported how many of the 19 total cases in the isoniazid arm were among adults).

For trials other than the IUAT trial to be included in this sensitivity analysis, we required that they either confirmed LTBI for subjects to be eligible, reported data for subjects with confirmed LTBI, or that the vast majority of subjects (>75%) were tuberculin positive. These trials met many of our eligibility criteria but used a longer duration of treatment than is currently recommended by the Centers for Disease Control and Prevention (i.e., ≥1 year of isoniazid), and some used lower or higher doses than currently recommended[42,43] or did not require LTBI confirmation for subjects to be eligible.[41,43,44] One of the four trials was rated poor quality.[42]

Abbreviations: CI=confidence interval; LTBI=latent tuberculosis infection; INH=isoniazid; IUAT=International Union Against Tuberculosis; mths=months; RR=relative risk.

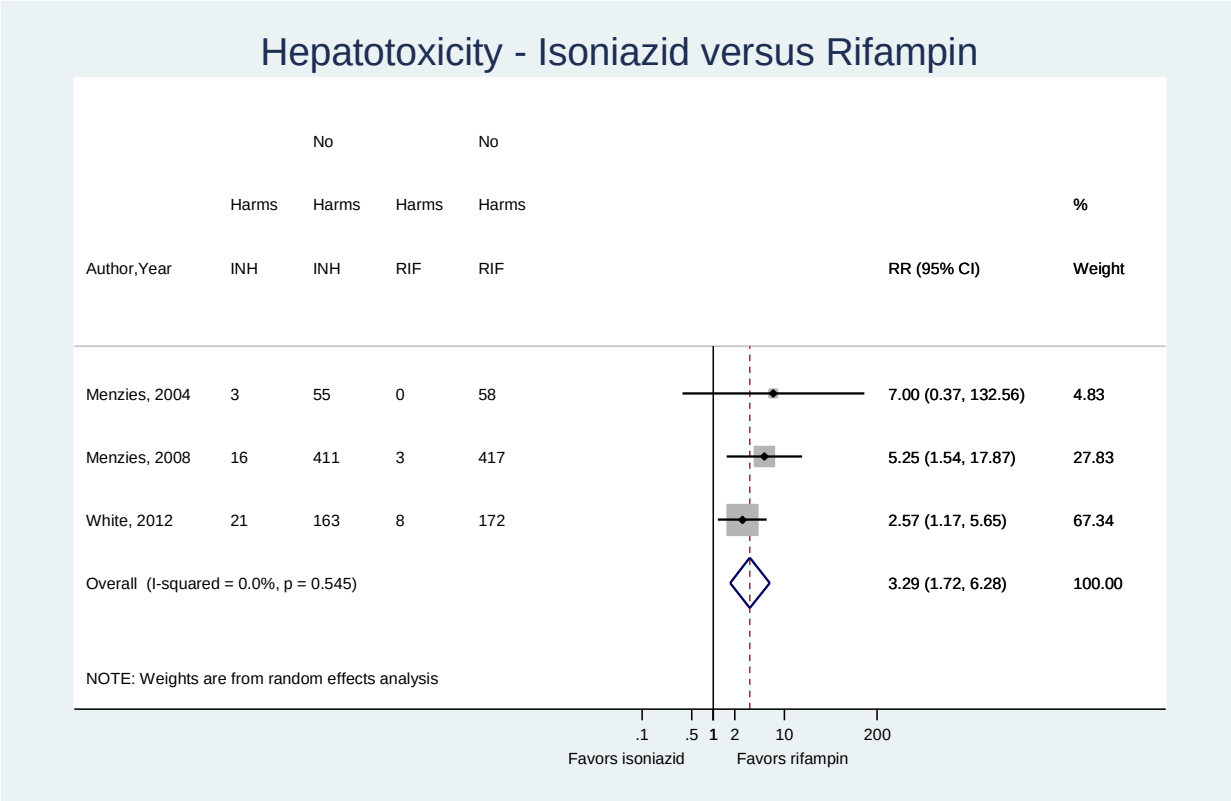
Figure 8. Isoniazid Compared With Placebo: Relative Risk of Developing Hepatotoxicity in the IUAT Trial



Notes: For Thompson 1982[135] (IUAT trial), we included data from the 12-, 24-, and 52-week groups. A definition for hepatotoxicity (presented as "hepatitis" in this study) was not reported.

Abbreviations: CI=confidence interval; INH=isoniazid; IUAT=International Union Against Tuberculosis; RR=relative risk.

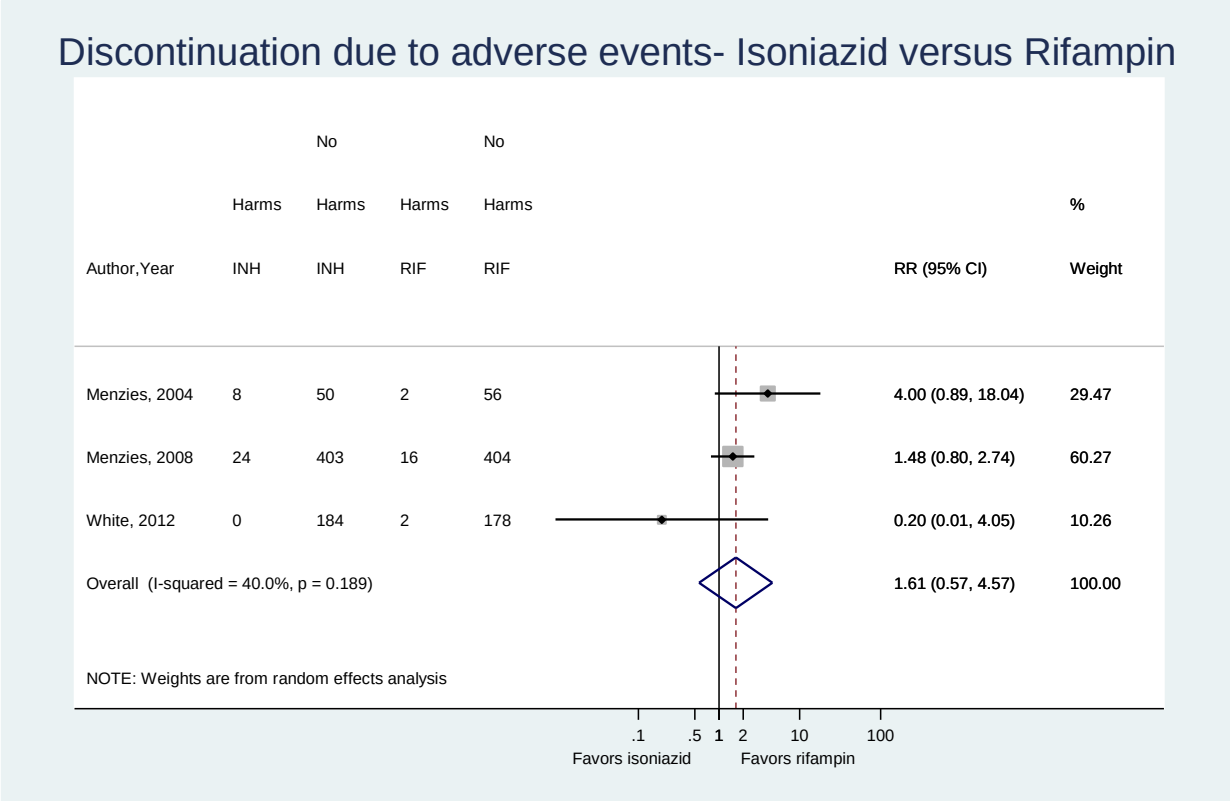
Figure 9. Isoniazid Compared With Rifampin: Relative Risk of Developing Hepatotoxicity, Data From Three Randomized, Controlled Trials



Notes: For Menzies 2004, hepatotoxicity was defined as liver transaminase (alanine transaminase) levels more than 3 times the upper limits of normal with symptoms, or transaminase levels more than 5 times the upper limits of normal without symptoms. For Menzies 2008, hepatotoxicity includes both grade 3 and grade 4 hepatotoxicity. Liver aminotransferase levels that increased to 5 to 10 or 3 to 10 times the upper limit of normal in the presence of compatible symptoms met criteria for grade 3 hepatotoxicity, whereas those that exceeded 10 times the upper limit of normal met criteria for grade 4 toxicity. For White 2012, hepatotoxicity was defined as liver function tests greater than 3 times the upper limit of normal.

Abbreviations: CI=confidence interval; INH=isoniazid; RIF=rifampin; RR=relative risk.

Figure 10. Isoniazid Compared With Rifampin: Relative Risk of Treatment Discontinuation Due to Adverse Events, Data From Three Randomized, Controlled Trials



Notes: For Menzies 2004, adverse events that resulted in permanent discontinuation of therapy were hepatitis, severe nausea and vomiting, persistent debilitating fatigue, and rash. For Menzies 2008, a blinded review panel judged the type and severity of the adverse event and its likely relationship to the study drug. The total presented reflects permanent discontinuation of therapy due to any adverse event (grade 1–4) judged to be probably drug related. These adverse events were hepatotoxicity, hematologic, drug interaction, rash, and gastrointestinal intolerance. For White 2012, treatment discontinuation adverse events were elevated liver function tests and nausea/vomiting.

Abbreviations: CI=confidence interval; INH=isoniazid; RIF=rifampin; RR=relative risk.

Table 1. Summary of Sensitivity Estimates for Various Thresholds of the Tuberculin Skin Test and Interferon-Gamma Release Assays Among Patients With Bacteriologic-Confirmed Tuberculosis

Test	Number of Studies (Total N)	Pooled Sensitivity Estimate (95% CI); I^2	Individual Study Sensitivity Estimate (95% CI); N
TST (5-mm threshold)	8 (803)	0.79 (0.69 to 0.89)*; 94.6%	See Figure 3
TST (10-mm threshold)	11 (988)	0.79 (0.71 to 0.87); 91.4%	See Figure 3
TST (15-mm threshold)	7 (740)	0.52 (0.35 to 0.68); 95.5%	See Figure 3
IGRA: T-SPOT.*TB*	16† (984)	0.90 (0.87 to 0.93); 63.6%	See Figure 4
IGRA: QFT-G	17 (1,073)	0.77 (0.74 to 0.81); 55.3%	See Figure 4
IGRA: QFT-GIT	24 (2,321)	0.80 (0.77 to 0.84); 74.3%	See Figure 4
IGRA: QFT-G and QFT-GIT	1	NA	0.71 (0.64 to 0.77); 181[97]

* Estimates from a maximum-likelihood random-effects model yielded slightly different estimate (0.84 [95% CI, 0.68 to 0.92]).

† One study[61] could not be included in the pooled estimate due to a point estimate for sensitivity of 1.0 (95% CI, 0.69 to 1.0). The estimate using the maximum likelihood approach, which can accommodate point estimates of 1.0, was similar (0.90 [95% CI, 0.86 to 0.93]).

Abbreviatons: CI=confidence interval; IGRA=interferon-gamma release assay; N=number of patients; NA=not applicable; QFT-G=QuantiFERON-TB Gold (2nd-generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd-generation test); TST=tuberculin skin test.

Table 2. Summary of Specificity Estimates for Various Thresholds of the Tuberculin Skin Test and Interferon-Gamma Release Assays Among Healthy Subjects Without Tuberculosis Exposures or Risks

Test	Number of Studies (Total N for Pooled Studies)	Pooled Specificity Estimate (95% CI); I^2	Individual Study Specificity Estimate (95% CI); N
TST (5-mm threshold)	4	NA*	0.30 (0.19 to 0.44); 47[69] 0.95 (0.94 to 0.96); 2,848[54] 0.94 (0.92 to 0.95); 1,750[122] 0.97 (0.95 to 0.98); 551[120]
TST (10-mm threshold)	9[†] (9,651)	0.97 (0.96 to 0.99); 94.3%	See Figure 5
TST (15-mm threshold)	12 (9,640)	0.99 (0.98 to 0.99); 91.7%	See Figure 5
IGRA: T-SPOT.*TB*	5 (1,810)	0.95 (0.92 to 0.98)[‡]; 79.1%	See Figure 5
IGRA: QFT-G	4 (699)	0.98[§] (0.90 to 1.0)	See Figure 5
IGRA: QFT-GIT	4 (2,053)	0.97 (0.94 to 0.99); 93.4%	See Figure 5

* Studies not pooled as one study estimate from an intermediate-TB-burden country was much lower than the estimates from low-TB-burden countries.

[†] One study[121] could not be included in the DerSimonian and Laird pooled estimate because of a point estimate for specificity of 1.0 (95% CI, 0.99 to 1.00). The estimate using the maximum likelihood approach, which can accommodate point estimates of 1.0, was similar (0.97 [95% CI, 0.93 to 0.99]).

[‡] Estimates from a maximum-likelihood random-effects model yielded a slightly different estimate (0.93 [95% CI, 0.85 to 0.97]).

[§] Pooled estimate is from a maximum-likelihood random-effects model because two studies included point estimates for specificity of 1.0. The I^2 statistic is not calculated when using this model.

Abbreviations: CI=confidence interval; IGRA=interferon-gamma release assay; N=number analyzed; NA=not applicable; QFT-G=QuantiFERON-TB Gold (2nd-generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd-generation test); TST=tuberculin skin test.

Table 3. Summary of Evidence of Accuracy and Reliability of the Tuberculin Skin Test and Interferon-Gamma Release Assays for Targeted* Screening of Latent Tuberculosis Infection (KQ 2a)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
TST 5-mm Accuracy	Sn: 8 (803) Sp: 4 (5,196) Observational studies of test accuracy	Sn pooled: 0.79 (95% CI, 0.69 to 0.89; I^2=94.6%) Sp in low-TB-burden countries: 0.94 (95% CI, 0.92 to 0.95) 0.95 (95% CI, 0.94 to 0.96) 0.97 (95% CI, 0.95 to 0.98) Sp in intermediate-TB-burden country: 0.30 (95% CI, 0.19 to 0.44)	Consistent but imprecise for Sn Consistent and precise for Sp in low-TB-burden countries	Undetected	Fair	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies	TST using Mantoux procedure with intermediate-strength dose of PPD Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk populations (Sp)
TST 10-mm Accuracy	Sn: 11 (988) Sp: 9 (9,651) Observational studies of test accuracy	Sn pooled: 0.79 (95% CI, 0.71 to 0.87; I^2=91.4%) Sp pooled: 0.97 (95% CI, 0.96 to 0.99; I^2=94.3%)[†]	Consistent but imprecise for Sn Consistent and precise for Sp in low-TB-burden countries	Undetected	Fair	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies	TST using Mantoux procedure with intermediate-strength dose of PPD Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk populations (Sp)
TST 15-mm Accuracy	Sn: 7 (740) Sp: 12 (9,640) Observational studies of test accuracy	Sn pooled: 0.52 (95% CI, 0.35 to 0.68; I^2=96.3%) Sp pooled: 0.99 (95% CI, 0.98 to 0.99; I^2=91.7%)[‡]	Inconsistent and imprecise for Sn Consistent and precise for Sp in low-TB-burden countries	Undetected	Fair	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies	TST using Mantoux procedure with intermediate-strength dose of PPD Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk populations (Sp) The 15-mm threshold is not recommended in current practice for patients at high risk for TB infection

Table 3. Summary of Evidence of Accuracy and Reliability of the Tuberculin Skin Test and Interferon-Gamma Release Assays for Targeted* Screening of Latent Tuberculosis Infection (KQ 2a)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
TST Reliability	Interrater reliability: 3 (3,142) Observational studies of test accuracy	Kappa: 0.69 and 0.79 in 2 studies assessing reliability of rater assessment of skin test reaction in healthy populations at low risk for TB Kappa: 0.52 to 0.78 of rater assessment of skin test reaction as assessed in different study with populations including subjects with active TB and healthy, low-risk subjects	Consistent for moderate to substantial agreement; precision unknown	Undetected	Fair	Reliability may be affected by the populations in which it is assessed	TST using Mantoux procedure with intermediate-strength dose of PPD TST administration and interpretation dependent on the use of appropriate, standardized technique
IGRA T-SPOT.*TB* Accuracy	Sn: 16 (984) Sp: 5 (1,810) Observational studies of test accuracy	Sn pooled: 0.90 (95% CI, 0.87 to 0.93; I^2=63.6%) Sp pooled: 0.95 (95% CI, 0.92 to 0.98; I^2=79.1%)[§]	Consistent and precise for Sn and Sp	Undetected	Fair	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies vary in how they report indeterminate results	Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk (Sp) populations T-SPOT.*TB* requires proper specimen handling prior to assay; interpretation of test can be done manually through visual inspection or through use of machines that automate interpretation FDA-approved threshold for positive test is higher than threshold used in non-U.S. studies

Table 3. Summary of Evidence of Accuracy and Reliability of the Tuberculin Skin Test and Interferon-Gamma Release Assays for Targeted* Screening of Latent Tuberculosis Infection (KQ 2a)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
IGRA T-SPOT.*TB* Reliability	Interrater reliability: 2 (404) Reproducibility: 1 (130) Test-retest: 2 (296) Observational studies of test accuracy	Study conducted in active TB patients with manual interpretation, interrater reliability: 96% (kappa=0.92); manual vs. automatic interpretation, interrater reliability: 85.8% (kappa=0.73) Study conducted in immigrants who were close contacts of active TB patients: kappa >0.6 among 6 manual readers Discordant results in participants who had 2 samples drawn simultaneously (same lab and method of interpretation): 10/153 (6.5%) Study enrolling health care workers : 9/111 (8.1%) tests changed from negative to positive and 10/19 (52.6%) changed from positive to negative at 2 weeks. Study enrolling Nepalese military recruits, kappa for agreement between initial test and retest=0.66 (95% CI, 0.50 to 0.83)	Consistent for interrater reliability, unknown precision Consistency unknown for single study, unknown precision Inconsistent and imprecise for test-retest reliability	Undetected	Fair	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies vary in how they report indeterminate results	T-SPOT.*TB* requires proper specimen handling prior to assay; interpretation of test can be done manually through visual inspection or through use of machine that automates interpretation

Table 3. Summary of Evidence of Accuracy and Reliability of the Tuberculin Skin Test and Interferon-Gamma Release Assays for Targeted* Screening of Latent Tuberculosis Infection (KQ 2a)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
IGRA QFT-G Accuracy	Sn: 17 (1,073) Sp: 4 (699) Observational studies of test accuracy	Sn pooled: 0.77 (95% CI, 0.74 to 0.81; I^2=55.3%) Sp pooled: 0.98¶ (95% CI, 0.90 to 1.0)	Consistent and precise for Sn Consistent and precise for Sp in low-TB-burden countries, imprecise in intermediate-TB-burden country	Undetected	Fair	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies vary in how they report indeterminate results	Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk (Sp) populations QFT-G requires proper specimen handling prior to assay This generation of QFT test is no longer being marketed
IGRA QFT-GIT Accuracy	Sn: 24 (2,321) Sp: 4 (2,053) Observational studies of test accuracy	Sn pooled: 0.80 (95% CI, 0.77 to 0.84; I^2=74.3%) Sp pooled: 0.97 (95% CI, 0.94 to 0.99; I^2=93.4%)	Consistent and precise for Sn Consistent and precise for Sp in low-TB-burden countries, imprecise in intermediate-TB-burden country	Undetected	Fair	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies vary in how they report indeterminate results	Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk (Sp) populations QFT-GIT requires proper specimen handling prior to assay

Table 3. Summary of Evidence of Accuracy and Reliability of the Tuberculin Skin Test and Interferon-Gamma Release Assays for Targeted* Screening of Latent Tuberculosis Infection (KQ 2a)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
IGRA QFT-GIT Reliability	Interrater reliability: 1 (146) Reproducibility: 1 (130) Test-retest reliability: 2 (296) Interlaboratory reliability: 1 (91) Observational studies of test accuracy	Across all 4 tests (2 samples from each participant analyzed by manual and automated ELISA): 88.6% were concordant (16% concordant positive and 72.6% concordant negative); 11% were discordant Discordance by method of interpretation: automated vs. automated: 4.8% (kappa=0.85); manual vs. manual: 6.9% (kappa= 0.80); automated vs. manual, 3.4% to 9.0% across comparisons (kappa=0.73 to 0.90) Number of discordant results in participants who had 2 samples drawn simultaneously: 10/172 (5.8%) Study enrolling health care workers, 10/134 (7.5%) results changed from negative to positive and 5/15 (33.3%) changed from positive to negative at 2 weeks. In the other study enrolling Nepalese military recruits, kappa for agreement between initial test and retest=0.48 (95% CI, 0.26 to 0.70) Across 3 labs, 7/91 (7.7%) subjects had discordant results; kappas of pairwise lab sample comparisons were 0.87, 0.89, and 0.93	Consistency unknown for single study assessing Interrater reliability, precision unknown Consistency unknown for single study assessing reproducibility, precision unknown Inconsistent and imprecise for test-retest reliability Consistency unknown for single study assessing interlaboratory reliability, precision unknown	Undetected	Fair	Studies vary in how they assess reliability outcomes	QFT-GIT requires proper specimen handling prior to assay

* Targeted refers to screening in subjects who have been identified as higher risk for infection; for example, recent arrivals (within the past 5 years) to the United States who were born in foreign countries.

† Pooled estimate includes one study conducted in an intermediate-TB-burden country with a much lower estimate (0.45) compared with the low-TB-burden countries included in the pooled estimate. The pooled estimate without this study was 0.98 (95% CI, 0.97 to 0.99; I^2=91.2%).

Table 3. Summary of Evidence of Accuracy and Reliability of the Tuberculin Skin Test and Interferon-Gamma Release Assays for Targeted* Screening of Latent Tuberculosis Infection (KQ 2a)

‡ Pooled estimates includes 2 studies in intermediate-TB-burden countries with much lower estimates (0.60 and 0.57) compared with low-TB-burden countries included in the pooled estimate. The pooled estimate without these studies was the same but I^2 was reduced to 88.7%.
§ Pooled estimate includes 2 low-, 2 intermediate-, and 1 mixed- (2 countries, 1 low- and 1 intermediate-) TB-burden countries. The estimates in the 2 intermediate-TB-burden countries were lower (0.85 and 0.73) compared with estimates in the other studies.
¶ Pooled estimate is from maximum-likelihood random-effects model since 2 studies included point estimates for specificity of 1.0. The I^2 statistic is not calculated when using this model.

Abbreviations: CI=confidence interval; FDA=U.S. Food and Drug Administration; ELISA=enzyme-linked immunosorbent assay; KQ=key question; LTBI=latent tuberculosis infection; PPD=purified protein derivative; QFT-G=QuantiFERON-TB Gold (2nd-generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd-generation test); Sn=sensitivity; Sp=specificity; TB=tuberculosis; TST= tuberculin skin test.

Table 4. Summary of Evidence for Treatment of Latent Tuberculosis Infection With CDC-Recommended Pharmacotherapy Treatment Regimens (KQ 3)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
INH vs. placebo	1 RCT (27,830)* Sensitivity analysis with 5 RCTs (36,823)	Developing active TB: *Main analysis* RR: 0.35 at 5 years followup (95% CI, 0.24 to 0.52) for INH x 24 weeks† compared to placebo; NNT=112 *Sensitivity analysis* RR: 0.31 at 2 to 10 years followup‡ (95% CI, 0.24 to 0.41)	Consistency NA for the single study; reasonably precise for developing active TB Consistent across 5 RCTs used in sensitivity analysis for developing active TB (I^2=0%); precise	Undetected	Good (fair to good for sensitivity analysis)	Studies used in sensitivity analysis used longer duration (1 year of INH)§ and some used doses lower or higher than currently recommended; 1 trial was poor quality for high risk of selection, attrition, and measurement bias and confounding	Study population in main analysis trial included those with fibrotic pulmonary lesions and a ≥6-mm TST; median age 50; trials in main and sensitivity analysis published >30 years ago (1963, 1965, 1968, 1978, 1982). Trials in sensitivity analysis enrolled HH contacts of active cases, veterans with inactive pulmonary TB, persons residing in mental institutions, and military members exposed to an active TB case.
	1 RCT (27,830)*	Deaths due to TB: 0 vs. 3; RR: 0.14 (95% CI, 0.01 to 2.78) for the combined isoniazid groups vs. placebo	Imprecise for deaths from TB	Undetected	Good	Small number of events	Same as above for main analysis applicability
	1 RCT (27,830)*	All-cause mortality: NR by group				Data on all-cause mortality NR by group	Same as above for main analysis applicability
RIF vs. INH	1 RCT (847)	Developing active TB: NR Deaths due to TB: 0 vs. 0 All-cause mortality: 0 vs. 1	Consistency NA, single study; imprecise	Undetected	Good	Open label. Lacking data for outcome of developing active TB, no events for outcome of deaths from TB, and only 1 event for all-cause mortality outcome	Adults with a positive TST and physician recommendation for INH in Canada, Saudi Arabia, and Brazil. Just over half were ages 18 to 34 and just over half were male. Trial focused on harm outcomes; subjects only followed for duration of their treatment (4 or 9 months).
RPT + INH vs. INH	1 RCT (6,886)¶	Developing active TB: 5 vs. 10** Deaths due to TB: NR All-cause mortality: 30 vs. 34; p=0.42	Consistency NA for this single study; reasonably precise for developing active TB and all-cause mortality. NR for deaths from TB.	Undetected	Fair	Open label; single study, no data for deaths due to TB	Median age 37; just over half male; 57% white; combined intervention was directly observed once weekly for 3 months; high-risk subjects; most had a close contact with an active TB case; 25% were included solely because of recent TST conversion

* Of the 27,830 participants in the IUAT trial, the only trial meeting all eligibility criteria for KQ 3 that compared INH with placebo, 6,965 were treated with a CDC-approved regimen (INH 300 mg x 24 weeks). The IUAT trial randomized 27,830 participants to INH 300 mg x 12 weeks (6,956), INH 300 mg x 24 weeks (6,965), INH 300 mg x 52 weeks (6,919), or placebo (6,990).

Table 4. Summary of Evidence for Treatment of Latent Tuberculosis Infection With CDC-Recommended Pharmacotherapy Treatment Regimens (KQ 3)

† The relative risks for the other treatment groups developing active TB compared with placebo were 0.79 (95% CI, 0.58 to 1.06) and 0.25 (95% CI, 0.16 to 0.39) for 12 and 52 weeks of INH, respectively.
‡ Followup for the 5 RCTs included in the sensitivity analysis ranged from 2 to 10 years; one study followed patients for 2 years (Bush), one for 5 years (IUAT), two for 7 years (Falk, Veening), and one for 10 years (Ferebee).
§ No longer a CDC-recommended treatment regimen.
¶ This open-label, noninferiority trial randomized 7,731 subjects; we obtained data from the CDC for this table on the subset of participants most directly relevant for this review: the 6,886 adults (age ≥18 years) who were HIV negative and were TST or IGRA positive.
** The combination therapy group was found to be noninferior to the INH-only group.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; HH=household; INH=isoniazid; IUAT=International Union Against Tuberculosis; KQ=key question; NA=not applicable; RCT=randomized, controlled trial; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis; TST= tuberculin skin test.

Table 5. Summary of Evidence for Harms Associated With CDC-Recommended Pharmacotherapy Treatment Regimens for Latent Tuberculosis Infection (KQ 5)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency /Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
INH vs. placebo	1 RCT (27,830)* Sensitivity analysis with 4 RCTs (35,161)	Hepatotoxicity: *Main analysis*: RR: 4.59 at 5 years (95% CI, 2.03 to 10.39) for 24 weeks INH compared to placebo; NNH=279 *Sensitivity analysis:* Pooled RR: 5.04† (95% CI, 2.50 to 10.15; I^2=0%)	Consistency NA for the single study in main analysis; consistent across 4 studies in sensitivity analysis; imprecise	Undetected	Fair for main analysis, fair to poor for sensitivity analyses	Harm ascertainment techniques not well described Studies used in sensitivity analysis limited by measurement and ascertainment bias	Study population in main analysis trial includes those with fibrotic pulmonary lesions and a ≥6-mm TST; median age 50; trial published in 1982. Trials in sensitivity analysis published in 1974, 1977, and 1978 and enrolled employees in a U.S. hospital, individuals meeting ATS criteria referred to a U.S. military medical center, and veterans with inactive pulmonary TB
	1 RCT (27,830)*	Death from hepatotoxicity‡: 0 in placebo group, 0.14 per 1,000 receiving INH; RR: 2.35 (95% CI, 0.12 to 45.46; NNH=6,947)	Consistency NA for the single study; imprecise	Undetected	Fair	Rare number of events Harm ascertainment techniques not well described	Same as above for main analysis
	1 RCT (27,830)*	Discontinuation of treatment due to adverse events: *Main analysis:* RR: 1.50† (95% CI, 1.18 to 1.89; NNH=167)	Consistency NA for the single study; reasonably precise.	Undetected	Fair for main analysis	Harm ascertainment techniques not well described	Same as above for main analysis
	Sensitivity analysis with 4 RCTs (55,398)	*Sensitivity analysis:* Pooled RR: 1.58 (95% CI, 1.00 to 2.49; I^2=70.2%)	Inconsistent across the 4 studies included in sensitivity analysis, reasonably precise	Undetected	Fair to poor for sensitivity analysis	Studies limited by lack of prespecification of harm outcomes, measurement and ascertainment bias	Trials in treatment discontinuation sensitivity analysis published in 1963, 1965, and 1977 and enrolled residents of mental institutions, HH contacts of active cases, and adults meeting ATS criteria for chemoprophylaxis
	1 RCT (27,830)*	GI adverse events: RR: 1.33† (95% CI, 1.01 to 1.75) *Sensitivity analysis:* Different outcomes reported across studies; no differences among groups	Consistency NA for the single study; reasonably precise	Undetected	Fair to poor	GI harms not prespecified, measurement and ascertainment bias	Study population in main analysis trial includes those with fibrotic pulmonary lesions and a ≥6-mm TST; median age 50; trial published in 1982

Table 5. Summary of Evidence for Harms Associated With CDC-Recommended Pharmacotherapy Treatment Regimens for Latent Tuberculosis Infection (KQ 5)

Test or Intervention	Number of Studies (Observations) Study Design by Test or Outcome	Summary of Findings by Test or Outcome	Consistency /Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	Applicability
INH vs. RIF	3 RCTs (1,327)	Hepatotoxicity: Pooled RR: 3.29 (95% CI, 1.17 to 6.28; I^2=0%) Death from hepatotoxicity: No events reported in any arms of any study	Consistent, imprecise	Undetected	Fair to good	2 trials were open-label, 1 trial lost nearly half of participants to followup	Trials published in 2004, 2008, 2012; subjects had positive TST following Canadian guidelines in 2 trials, subjects in other trial were inmates diagnosed with LTBI at jail entry
		Discontinuation of treatment due to adverse events: Pooled RR: 1.61 (95% CI, 0.57 to 4.57; I^2=40.0%)	Inconsistent, imprecise				
	2 RCTs (1,211)	GI adverse events: Pooled RR: 1.60 (95% CI, 0.76 to 3.40; I^2=0%)	Inconsistent, imprecise	Undetected	Fair	1 study lost nearly half of participants to followup; duration of followup may be inadequate for harms	Trials published in 2008 and 2012; subjects had positive TST following Canadian guidelines in 1 trial, subjects in other trial were inmates diagnosed with LTBI at jail entry
	2 RCTs (480)	Other adverse events: Pooled RR: 0.82 (95% CI, 0.42 to 1.59; I^2=0%)	Inconsistent, imprecise	Undetected	Fair	1 study lost nearly half of participants to followup; duration of followup may be inadequate for harms, measurement and ascertainment bias	Trials published in 2004 and 2012; subjects had positive TST following Canadian guidelines in 1 trial, subjects in other trial were inmates diagnosed with LTBI at jail entry
RPT + INH vs. INH	1 RCT (6,886)[§]	Hepatotoxicity (grade 3 or 4): Calculated RR: 0.90 (95% CI, 0.75 to 1.08) Death from hepatotoxicity: 0.83 (95% CI, 0.51 to 1.35)	Consistency NA for the single study, imprecise	Undetected	Fair	Single study, masking unclear and high overall attrition	Trial published in 2011, data were from HIV-negative subgroup with TST or IGRA confirmation; combined intervention was directly observed once week x 3 months; high-risk individuals; most had close contact with an active TB case; 25% were included solely because of recent TST conversion
		Discontinuation of treatment due to adverse events: Calculated RR: 1.28 (95% CI, 1.03 to 1.59)	Consistency NA for the single study, reasonably precise				
		Possible hypersensitivity: RR: 8.04 (95% CI, 4.88 to 13.26)	Consistency NA for the single study, imprecise				

* Of the 27,830 participants in the IUAT trial, the only trial meeting all eligibility criteria for KQ 3 that compared INH with placebo, 6,965 were treated with a CDC-approved regimen (INH 300 mg x 24 weeks). The IUAT trial randomized 27,830 participants to INH 300 mg x 12 weeks (6,956), INH 300 mg x 24 weeks (6,965), INH 300 mg x 52 weeks (6,919), or placebo (6,990).

† Estimate includes combined data from all three INH study arms (12 weeks, 24 weeks, 52 weeks) in the IUAT trial.

Table 5. Summary of Evidence for Harms Associated With CDC-Recommended Pharmacotherapy Treatment Regimens for Latent Tuberculosis Infection (KQ 5)

[‡] One additional RCT used in sensitivity analysis for this outcome reported no deaths from hepatotoxicity in either the INH or placebo arm.
[§] Followup for the 5 RCTs included in the sensitivity analysis ranged from 2 to 10 years; one study followed patients for 2 years (Bush), one for 5 years (IUAT), two for 7 years (Falk, Veening), and one for 10 years (Ferebee).

Abbreviatons: ATS=American Thoracic Society; CDC=Centers for Disease Control and Prevention; CI=confidence interval; KQ=key question; IGRA=interferon-gamma release assay; INH=isoniazid; IUAT=International Union Against Tuberculosis; LTBI=latent tuberculosis infection; NA=not applicable; NNH=number needed to harm; RCT=randomized, controlled trial; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis; TST=tuberculin skin test.

Table 6. Projected 5-Year Outcomes of Screening 100,000 Asymptomatic Adults for Latent Tuberculosis Infection[a]

Outcome	Variable	Foreign-Born Population Screened	Foreign-Born Population Not Screened	Community, Noninstitutionalized Population Screened	Community, Noninstitutionalized Population Not Screened
Detection	Patients with LTBI[b], n (95% CI)	20,500 (16,100 to 25,800)	20,500 (16,100 to 25,800)	4,700 (3,400 to 6,300)	4,700 (3,400 to 6,300)
	Positive screening test, chest x-ray, and offered LTBI treatment[c], n (n false positive/n true positive)	18,580 (2,385/16,195)	NA	6,572 (2,859/3,713)	NA
Benefits	Progression to active TB[d], n (n false positive/n true positive) [range of estimate][e]	79 (0/79) [62 to 99]	225 (NA) [177 to 287]	18 (0/18) [13 to 24]	52 (NA) [37 to 69]
	NNT to prevent 1 case of LTBI from progressing to active TB[f]	111		111	
	Progression to active TB using alternative assumption for rate of LTBI reactivation[g], n (n false positive/n true positive) [range of estimate][e]	28 (0/28) [19 to 35]	79 [55 to 100]	5 (0/5) [4 to 7]	16 (NA) [11 to 21]
	NNT to prevent 1 case of LTBI from progressing to active TB under alternative assumption for rate of LTBI reactivation[f,g]	314		366	
	TB transmission	Unknown	Unknown	Unknown	Unknown
	Death from TB	Unknown	Unknown	Unknown	Unknown
Harms	Hepatotoxicity[h] (INH or placebo), n (n false positive/n true positive) [range of estimate][e]	85 (11/74) [70 to 104]	19 (NA) [15 to 23]	30(13/17) [26 to 36]	7 (NA) [6 to 8]
	NNH to cause hepatotoxicity from treatment with INH[i]	279		279	
	Hepatotoxicity (RIF or placebo)[j], n (n false positive/n true positive) [range of estimate][e]	26 (3/23) [21 to 32]	19 (NA) [15 to 23]	9 (4/5) [8 to 11]	7 (NA) [6 to 8]
	NNH to cause hepatotoxicity from treatment with RIF[i]	2,531		2,531	
	Discontinuation due to adverse effects (INH or placebo)[k], n (n false positive/n true positive) [range of estimate][e]	334 (43/292) [274 to 407]	223 (NA) [183 to 271]	118 (51/67) [101 to 140]	79 (NA) [67 to 93]
	NNH to cause discontinuation due to adverse events from treatment with INH	167		167	
	Potential psychological harms	Unknown		Unknown	

Table 6. Projected 5-Year Outcomes of Screening 100,000 Asymptomatic Adults for Latent Tuberculosis Infection[a]

Outcome	Variable	Foreign-Born Population Screened	Foreign-Born Population Not Screened	Community, Noninstitutionalized Population Screened	Community, Noninstitutionalized Population Not Screened
Summary of estimated benefits and harms		52 to 146 active TB cases prevented[l] 67 cases of hepatotoxicity caused if using INH for everyone; 9 of those cases caused by unnecessary treatment (for persons with false positives)[m] 7 cases of hepatotoxicity caused if using RIF for everyone; 1 of those cases caused by unnecessary treatment (for persons with false positives)[m] 111 cases of discontinuation due to adverse events caused if using INH for everyone; 14 of those caused by unnecessary treatment (for persons with false positives)[m]		10 to 33 active TB cases prevented[l] 24 cases of hepatotoxicity caused if using INH for everyone; 10 of those cases caused by unnecessary treatment (for persons with false positives)[m] 3 cases of hepatotoxicity caused if using RIF for everyone; 1 of those cases caused by unnecessary treatment (for persons with false positives)[m] 39 cases of discontinuation due to adverse events caused if using INH for everyone; 17 of those caused by unnecessary treatment (for persons with false positives)[m]	

[a] Projected benefits and harms were determined for persons in whom screening had not previously been performed and who would be eligible for and offered treatment for LTBI based on a positive screening test. When relevant, projected outcomes are shown as overall and in parentheses for persons with false-positive tests and those with true-positive tests, to illustrate how many persons would undergo unnecessary intervention with resulting harm.
[b] The prevalence of LTBI is 4.7% and 20.5% for the U.S. overall population and foreign-born U.S. population, respectively, based on 2011–2012 NHANES.[20] We use the foreign-born U.S. population as an example of outcomes among a higher-risk population because available estimates of prevalence and progression are readily available for this population, unlike other high-risk populations.
[c] Based on sensitivity (0.79) and specificity (0.97) for TST with 10-mm threshold for positive test, which is the threshold recommended for recent arrivals (within past 5 years) to the United States from high-risk areas based on current CDC recommendations.[12] A small proportion of those x-rayed will have findings suggestive of active TB disease and will go on to receive further diagnostic evaluation and treatment. A precise estimate of this proportion is not available and we have assumed it to be zero.
[d] Estimates for benefits were based on the IUAT trial, which may have limited applicability to current clinical practice because the study population was composed of subjects with pulmonary fibrotic lesions. Rate of progression in the absence of treatment at 5 years was 1.39% in the placebo arm and 0.5% in the 24-week isoniazid treatment arm, for a relative risk reduction of 0.35. Patients with false-positive or false-negative screening results receive no benefit from treatment, thus progression to active TB is only relevant for true positives.
[e] This range is an estimate based on the lower and upper bounds of the 95% CI, for prevalence. That is, it provides the range of possible estimates given the precision of the LTBI prevalence estimates available.
[f] Number needed to treat is calculated as 1/absolute risk reduction between treatment and control groups.
[g] Because using the rate of progression to active TB from the IUAT trial may not reflect contemporary risk, we also used a more recent estimate based on the rate of nonclustered TB cases, a proxy for reactivation. The rate of progression is estimated at 0.084/100 person-years for the overall U.S. population and 0.098/100 person-years for the foreign-born U.S. population.[8] We assumed the same relative risk reduction for treatment with isoniazid from the IUAT trial (0.35).
[h] We used rate of hepatotoxicity from the IUAT trial: 0.1% in the placebo group and 0.46% in the 24-week INH treatment group.[135]

Table 6. Projected 5-Year Outcomes of Screening 100,000 Asymptomatic Adults for Latent Tuberculosis Infection[a]

[i] Number needed to harm is calculated as 1/absolute harm risk difference between treatment and control groups.
[j] Estimates of hepatotoxicity in the studies evaluating isoniazid vs. rifampin reported hepatotoxicity rates over a different time period, using different definitions, were conducted nearly 30 years after the IUAT trial, and the event rate in the INH treatment arm was much higher than the rates reported in the IUAT trial, likely because these studies were designed specifically to evaluate harms. For these reasons, these rates could not be directly used in this outcomes table to compare with the NNT calculated from the IUAT trial. Thus, we used the pooled RR for hepatotoxicity for INH vs. RIF of 3.29 from our meta-analysis to adjust the IUAT trial rate for hepatotoxicity among the INH-treated arm to obtain an indirect estimate of a 5-year risk of hepatotoxicity from RIF compared with placebo of 0.14%.
[k] We used estimates of discontinuation of treatment due to adverse events from the IUAT trial.[135]
[l] This range includes an estimate based on rates of LTBI progression in the absence of treatment from the IUAT trial and an estimate based on a more recent lower estimate of the rate of progression in the absence of treatment.
[m] Unnecessary treatment is determined by the number of persons for whom a false-positive test resulted in treatment that is unnecessary and for which they have no potential to benefit.

Abbreviations: CDC=Centers for Disease Control and Prevention; CI=confidence interval; INH=isoniazid; IUAT=International Union Against Tuberculosis; LTBI=latent tuberculosis infection; NA=not applicable; NHANES=National Health and Nutrition Examination Survey; NNH=number needed to harm; NNT=number needed to treat; RIF=rifampin; RR=relative risk; TB=tuberculosis; TST=tuberculin skin test.

Appendix A Table 1. Prevalence of Latent Tuberculosis Infection by High-Risk Category From Published Studies in English, French, or Spanish, 2009 Through 2014[a]

High-Risk Description	Prevalence Based on TST ≥5 mm Median (Range)	Prevalence Based on T-SPOT.*TB* Median (Range)	Prevalence Based on QFT-GIT Median (Range)	Incidence of Active TB Median Rate per 1,000 (Range)
High risk because of increased likelihood of TB exposure				
Prisoners	45.5 (23.1–87.6)	NR	NR	2.6 (0.03–9.8)
Health care workers	29.5 (1.4–97.6)	5.2 (3.5–28.7)	14.1 (0.9–76.7)	1.3 (0.4–4.1)
Adult contacts of active TB cases	26.3 (1.8–82.7)	48.0 (29.6–59.6)	21.1 (6.6–55.1)	0.6[b]
Immigrants from high-TB-burden countries	39.7 (17.8–55.4)	17.0 (9.0–24.9)	30.2 (9.8–53.8)	3.6 (1.3–41.2)
Illicit drug users	85.0 (0.3–86.7)	45.8 (34.1–57.5)	63.0 (1.4–66.4)	6.0[b]
Homeless persons	45.6 (20.5–79.8)	NR	53.8 (18.6–75.9)	2.2 (0.1–4.3)
High risk because of underlying medical conditions				
HIV infection	19.2 (2.1–54.8)	11.3 (4.3–67.6)	14.5 (2.7–21.5)	16.2 (12.4–28.0)
Use of TNF-alpha blockers	18.6 (11.3–68.2)	20.0 (12.9–25.0)	11.8 (4.0–22.3)	1.4[b]
Silicosis	NR	61.0[b]	46.6[b]	32.1[b]
Organ transplantation	7.7 (4.4–21.9)	29.5 (20.5–38.5)	21.9 (16.4–23.5)	5.1[b]
Hemodialysis	21.9 (2.6–42.1)	43.6 (23.3–58.2)	33.4 (17.4–44.2)	26.6 (1.3–52.0)

[a] Adapted from Getahun et al, 2015.[9]
[b] Single study.

Abbreviations: HIV=human immunodeficiency virus; NR=not reported; QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd-generation test); TB=tuberculosis; TNF=tumor necrosis factor; TST=tuberculin skin test.

Appendix A Table 2. Recommended Treatment Regimens for Latent Tuberculosis Infection

Drug(s)	Duration	Dose	Frequency	Total Doses
INH	9 months	5 mg/kg Maximum dose: 300 mg	Daily	270
		15 mg/kg Maximum dose: 900 mg	Twice weekly[a]	76
	6 months	5 mg/kg Maximum dose: 300 mg	Daily	180
		15 mg/kg Maximum dose: 900 mg	Twice weekly[a]	52
INH and RPT	3 months	INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg, 900 mg maximum	Once weekly[a]	12
RIF	4 months	10 mg/kg Maximum dose: 600 mg	Daily	120

[a] Intermittent regimens must be provided via directly observed therapy (i.e., health care worker observes the ingestion of medication).

Abbreviations: INH=isoniazid; RIF=rifampin; RPT=rifapentine.

Appendix B. Detailed Methods

Search Strategies

Initial searches

PubMed (08/29/14)
Tuberculosis final searches, 8-29-14: 4,288 citations saved in EndNote
PubMed: 3,531 total English language citations saved in EndNote

Search	Query	Items found
#1	Search ("Tuberculosis"[Mesh] OR "Latent Tuberculosis"[Mesh])	159183
#2	Search ("Interferon-gamma Release Tests"[Mesh] OR IGRA[All Fields] OR "Mantoux tuberculin skin test"[All Fields] OR "Tuberculin Test"[Mesh] OR "tuberculin skin test"[All Fields] OR TST[tiab] OR "T-SPOT"[All Fields] OR "T-SPOT.TB"[All Fields] OR QuantiFERON[All Fields] OR "QFT-GIT"[All Fields])	15573
#3	Search (#1 and #2)	9057
#4	Search (#1 and #2) Filters: Humans	7781
#5	Search (#1 and #2) Filters: Systematic Reviews; Humans	151
#6	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	576514
#7	Search (#4 and #6)	176
#8	Search ("Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study” OR “observational studies”)	1820788
#9	Search (#4 and #8)	1800
#10	Search ("Isoniazid"[Mesh] OR isoniazid[All Fields] OR "rifapentine"[Supplementary Concept] OR rifapentine[All Fields] OR "Rifampin"[Mesh] OR Rifampin[All Fields])	32885
#11	Search (#1 and #10)	12750
#12	Search (#1 and #10) Filters: Humans	10205
#13	Search (#1 and #10) Filters: Systematic Reviews; Humans	155
#14	Search (#12 and #6)	684
#15	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study” OR “observational studies”)	1820788
#16	Search (#12 and #15)	1811
#17	Search (#5 or #13)	282
#18	Search (#5 or #13) Filters: English	243
#19	Search (#17 not #18)	39
#20	Search (#7 or #9 or #14 or #16)	4013
#21	Search (#7 or #9 or #14 or #16) Filters: English	3348
#22	Search (#20 not #21)	665
#23	Search (#18 or #21)	3531
#24	Search (#19 or #22)	703

Appendix B. Detailed Methods

Cochrane Library (08/29/14)
For the Cochrane Library search, we did not limit using study design terms, because Cochrane breaks out study results by the categories we seek. We searched the Cochrane Library of Reviews, Trials, Methods, and Technology Assessments. We did not save the Economic Evaluations.

Results
Screening:
All = 250 total results (179 without Economic Evaluations)
Cochrane Reviews = 12, all imported
Other reviews = 27, all imported
Trials = 136
Technology Assessments = 4
Economic Evaluations = 71 (not saved)

Drug therapy:
All = 714 total results (638 without Economic Evaluations)
Cochrane Reviews = 22, 11 imported
Other reviews = 36, 34 imported
Trials = 580, 533 imported
Economic Evaluations = 76 (not saved)

Importing to EndNote = 84 total reviews
673 Trials and Technology Assessments

Total in EndNote from the Cochrane Library = 757
ClinicalTrials.gov search 4-27-15
291 trials
Tuberculosis AND ("Interferon-gamma Release Tests" OR IGRA OR "Mantoux tuberculin skin test" OR "Tuberculin Test" OR "tuberculin skin test" OR TST or "T-SPOT" OR "T-SPOT.TB" or QuantiFERON or "QFT-GIT" OR isoniazid OR rifapentine OR Rifampin)

WHO ICTRP search and results (05/19/15)
185 records for 173 trials
Searched in Advanced search:
Condition box: Tuberculosis
Intervention box: Interferon-gamma Release Tests OR IGRA OR Mantoux tuberculin skin test OR Tuberculin Test OR tuberculin skin test OR TST or T-SPOT OR T-SPOT.TB or QuantiFERON or QFT-GIT OR isoniazid OR rifapentine OR Rifampin
(Recruitment status ALL)
185 records for 173 trials found

Bridge Searches

Tuberculosis update searches, July 30-31, 2015 and Aug 3, 2015
PubMed (07/30/15)

Search	Query	Items found
#1	Search ("Tuberculosis"[Mesh] OR "Latent Tuberculosis"[Mesh])	162959
#2	Search ("Interferon-gamma Release Tests"[Mesh] OR IGRA[All Fields] OR "Mantoux tuberculin skin test"[All Fields] OR "Tuberculin Test"[Mesh] OR "tuberculin skin test"[All Fields] OR TST[tiab] OR "T-SPOT"[All Fields] OR "T-SPOT.TB"[All Fields] OR QuantiFERON[All Fields] OR "QFT-GIT"[All Fields])	16219
#3	Search (#1 and #2)	9413
#4	Search (#1 and #2) Filters: Humans	8116
#5	Search (#1 and #2) Filters: Systematic Reviews; Humans	163

Appendix B. Detailed Methods

Search	Query	Items found
#6	Search ((randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	608085
#7	Search (#4 and #6)	184
#8	Search ("Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study” OR “observational studies”)	1946601
#9	Search (#4 and #8)	1945
#10	Search ("Isoniazid"[Mesh] OR isoniazid[All Fields] OR "rifapentine"[Supplementary Concept] OR rifapentine[All Fields] OR "Rifampin"[Mesh] OR Rifampin[All Fields])	33825
#11	Search (#1 and #10)	13136
#12	Search (#1 and #10) Filters: Humans	10571
#13	Search (#1 and #10) Filters: Systematic Reviews; Humans	170
#14	Search (#12 and #6)	708
#15	Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR “observational study” OR “observational studies”)	1946601
#16	Search (#12 and #15)	1931
#17	Search (#5 or #13)	309
#18	Search (#5 or #13) Filters: English	270
#19	Search (#17 not #18)	39
#20	Search (#7 or #9 or #14 or #16)	4285
#21	Search (#7 or #9 or #14 or #16) Filters: English	3604
#22	Search (#20 not #21)	681
#23	Search (#18 or #21)	3813
#24	Search (#19 or #22)	719
#25	Search (child* OR children OR teen OR teens OR teenage OR teenaged OR adolescen* OR pediatric OR paediatric* OR boys OR girls OR youth OR youths)	3221593
#26	Search (#5 or #13) Filters: English; Child: birth-18 years	67
#27	Search (#18 and #25)	84
#28	Search (#27 or #26)	84
#29	Search (#5 or #13) Filters: English; Adult: 19+ years	65
#30	Search (#28 and #29)	39
#31	Search (#28 NOT #30)	45
#32	Search (#18 NOT #31)	225
#33	Search (#28 NOT #30) Filters: Publication date from 2014/03/29	4
#34	Search (#18 NOT #31) Filters: Publication date from 2014/03/29	11
#35	Search (#19 and #25)	12
#36	Search (#17 not #18) Filters: Child: birth-18 years	10
#37	Search (#35 or #36)	12
#38	Search (#17 not #18) Filters: Adult: 19+ years	10
#39	Search (#37 and #38)	8
#40	Search (#37 NOT #39)	4
#41	Search (#37 NOT #40)	8
#42	Search (#7 or #9 or #14 or #16) Filters: Publication date from 2014/03/29; English	200
#43	Search (#7 or #9 or #14 or #16) Filters: Publication date from 2014/03/29; English; Child: birth-18 years	84
#44	Search (#42 and #25)	85

Appendix B. Detailed Methods

Search	Query	Items found
#45	Search (#43 or #44)	87
#46	Search (#7 or #9 or #14 or #16) Filters: Publication date from 2014/03/29; English; Adult: 19+ years	143
#47	Search (#45 and #46)	58
#48	Search (#45 NOT #47)	29
#49	Search (#46 NOT #48)	143
#50	Search (#19 or #22) Filters: Publication date from 2014/03/29	12
#51	Search (#19 or #22) Filters: Publication date from 2014/03/29; Child: birth-18 years	4
#52	Search (#50 and #25)	4
#53	Search (#19 or #22) Filters: Publication date from 2014/03/29; Adult: 19+ years	6

Cochrane Library (08/03/15)
Adults+ = **10**
4 Cochrane Reviews
6 Trials
Children = **21**
8 Reviews
3 Cochrane Reviews
5 Other reviews
8 Trials
1 Technology Assessment
4 Econ Evaluations (not saved)

ID	Search	Hits
#1	[mh Tuberculosis] or [mh "Latent Tuberculosis"]	1766
#2	[mh "Interferon-gamma Release Tests"] or IGRA or "Mantoux tuberculin skin test" or [mh "Tuberculin Test"] or "tuberculin skin test" or TST or "T-SPOT" or "T-SPOT.TB" or QuantiFERON or "QFT-GIT"	699
#3	#1 and #2	260
#4	[mh Isoniazid] or isoniazid or rifapentine or [mh Rifampin] or Rifampin	1918
#5	#1 and #4	740
#6	#3 or #5 Publication Year from 2014 to 2015	31
#7	(child* or children or teen or teens or teenage or teenaged or adolescen* or pediatric or paediatric* or boys or girls or youth or youths)	172203
#8	#6 and #7	16
#9	#6 and (adult* or middle-age* or elderly)	19
#10	#9 and #8, Adults+	10
#11	#6 not #10, Children	21

WHO ICTRP search and results
(6/9/15 – 8/3/15)
0 results
Searched in Advanced search:
Condition box: Tuberculosis
Intervention box:
Interferon-gamma Release Tests OR IGRA OR Mantoux tuberculin skin test OR Tuberculin Test OR tuberculin skin test OR TST or T-SPOT OR T-SPOT.TB or QuantiFERON or QFT-GIT OR isoniazid OR rifapentine OR Rifampin
(Recruitment status ALL)

ClinicalTrials.gov search update (08/03/15)
Last Updated Date: 4/27/15-08/03/15
39 trials
11 child
28 adult

Tuberculosis AND ("Interferon-gamma Release Tests" OR IGRA OR "Mantoux tuberculin skin test" OR "Tuberculin Test" OR "tuberculin skin test" OR TST or "T-SPOT" OR "T-SPOT.TB" or QuantiFERON or "QFT-GIT" OR isoniazid OR rifapentine OR Rifampin)

Appendix B. Eligibility Criteria for Studies by Key Question

Population	Intervention and Comparator	Setting	Outcomes	Study Design
KQ 1. Effect of screening for LTBI on morbidity, mortality, quality of life, and transmission				
Asymptomatic adults belonging to populations at increased risk for LTBI.[a] The following are excluded: children, symptomatic adults, close contacts of active TB patients, and populations at highest risk for progression from LTBI to active TB disease because of underlying immunosuppression or for whom LTBI screening and treatment would be part of standard disease management by specialty care providers. This includes people with HIV, head and neck cancer, leukemia or lymphoma, silicosis, history of or planned organ transplant, dialysis, planned or active use of TNF-α inhibitors, and planned or active use of chemotherapy. Mixed populations can be included if results are stratified for the included portion of the study population or the excluded portion does not exceed 25% of the study population.	Screening with TST or IGRA as compared with no screening. Studies with no comparator group are excluded.	Primary care settings in countries categorized as "Very High" on the Human Development Index (as defined by the United Nations Development Programme). Study settings considered to be applicable to primary care will also include homeless shelters, correctional facilities, college health settings, long-term care facilities, public health clinics, and workplaces. HIV and subspecialty care settings and workplace settings that screen for LTBI as part of a formal surveillance program for occupational exposure are excluded.	Active TB disease, TB transmission, quality of life, and mortality (disease-specific and overall). Other outcomes are excluded.	RCTs, prospective cohort studies. Other study designs are excluded.
KQ 2a. Accuracy and reliability of TST and IGRA screening tests **KQ 2b. Accuracy and reliability of sequential screening strategies using TST and IGRA screening tests**				
For sensitivity outcome: patients with bacteriologic-confirmed active TB who have not yet received treatment or who had received no more than a few weeks of treatment. Subjects with TB infection not confirmed by culture, AFB smear, or molecular tests are excluded. For specificity outcome: healthy subjects with no history of TB exposure or risks. Subjects with known history of TB or TB exposure, subjects with HIV, and acutely ill subjects are excluded. Mixed populations of children and adults or studies with both HIV-negative and HIV-positive subjects (sensitivity outcome only) can be included if results are stratified for the includable portion of the study population or the excluded portion does not exceed 25% of the study population.	TST using Mantoux method with intermediate-strength dose of PPD (i.e., 5 TU PPD-S, 2.5 TU RT-23) and standard thresholds for positive test (i.e., 5-mm, 10-mm, 15-mm). Commercially available, FDA-approved IGRA tests. T-SPOT.*TB*; QuantiFERON-TB Gold (2nd-generation); and QuantiFERON-TB Gold In-Tube (3rd-generation). Other tests, such as nucleic acid amplification, are excluded.	For sensitivity outcome: studies in any country in any setting are included. For specificity outcome: studies in intermediate- or low-TB-burden countries are included. Studies in high-TB-burden countries are excluded.[b]	Sensitivity, specificity, and reliability (i.e., test-retest). Concordance rates among tests and other outcomes are excluded. Studies assessing 2-step TST testing were excluded.	Systematic reviews, RCTs, cohort studies, cross-sectional studies. Other study designs are excluded.

Appendix B. Eligibility Criteria for Studies by Key Question

Population	Intervention and Comparator	Setting	Outcomes	Study Design
KQ 3. Effectiveness of treatment for LTBI				
Asymptomatic adults with confirmed LTBI; otherwise, same criteria as for KQ 1 except that close contacts of active TB patients were eligible if LTBI was confirmed (e.g., with a positive TST).	Treatment with CDC-recommended regimen (isoniazid daily for 6 or 9 months, isoniazid twice weekly by directly observed therapy for 6 or 9 months, rifampin daily for 4 months, or isoniazid plus rifapentine weekly by directly observed therapy for 3 months) compared with no treatment, delayed treatment, or another eligible treatment. Studies comparing other treatments or combinations are excluded.	Same as KQ 1, except that workplace settings were eligible.	Active TB disease (i.e., progression to active TB disease), TB transmission, quality of life, and mortality (disease-specific and overall).	RCTs
KQ 4. Harms of screening for LTBI				
Same as KQ 1	TST and IGRA tests as described in KQ 1 and KQ 2.	Same as KQ 1	False-positive results leading to unnecessary testing or treatment, labeling, stigma, anxiety, and cellulitis	Systematic reviews; RCTs and prospective cohort studies.
KQ 5. Harms of treatment for LTBI				
Same as KQ 3	Same as KQ 3	Same as KQ 1, except that workplace settings were eligible	Hepatotoxicity, mortality from hepatotoxicity, nausea, vomiting, peripheral neuropathy, development of drug-resistant TB, and other specific adverse effects of medications.	RCTs, prospective cohort studies, and case-control studies.

[a] Adult population subgroups at increased risk for developing active TB include: 1) people who have immigrated from TB-endemic countries; 2) people who work or reside in facilities or institutions with high-risk individuals, such as homeless shelters, correctional facilities, nursing homes or residential facilities; and 3) people with increased risk for progression from LTBI to active TB due to underlying illness or use of medications, injection drug use, or radiographic evidence of prior healed TB.[1]

[b] High-TB-burden countries include the following: Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Vietnam and Zimbabwe. This list is not exhaustive but represents the countries with the highest absolute burden (high rates and high population).[30]

Appendix B. Eligibility Criteria for Studies by Key Question

Abbreviations: AFB=acid fast bacilli; CDC=Centers for Disease Control and Prevention; FDA=U.S. Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; KQ=key question; LTBI=latent tuberculosis infection; PPD=purified protein derivative; RCT=randomized, controlled trial; TB=tuberculosis; TNF-α=tumor necrosis factor-alpha; TST=tuberculin skin test; TU=tuberculin units.

Appendix B. U.S. Preventive Services Task Force Quality Rating Criteria

Randomized, Controlled Trials

Criteria

- Initial assembly of comparable groups: Randomized controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: Equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good:
- Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis.

Fair:
- Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor:
- Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Sources: U.S. Preventive Services Task Force, Procedure Manual, Appendix VII http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii, Harris et al., 2001[31]

Studies of Diagnostic Tests

Criteria

- Screening test relevant, available for primary care, adequately described. Although this is one of the USPSTF criteria in its procedures manual, this criterion was not relevant for studies of sensitivity because no reference standard for LTBI exists and the population for sensitivity outcomes are patients with bacteriologic-confirmed active TB.
- Study uses a credible reference standard, performed regardless of test results.
- Reference standard interpreted independently of screening test.
- Handles indeterminate results in a reasonable manner.
- Spectrum of patients included in study. Although a USPSTF criterion, this criterion was also not relevant for this topic, given the very specific nature of the population required to estimate sensitivity and specificity in the absence of a reference standard for LTBI.
- Sample size: Although this is one of the criteria listed in the current procedures manual, we did not consider sample size when assessing study quality, as sample size affects precision of the estimate.
- Administration of reliable screening test: We also did not consider this criterion, as reliability was itself a separate outcome in this review.

- In addition to the criteria listed in the USPSTF procedures manual, we also considered whether patient selection criteria were clearly described, whether withdrawals were explained, and whether the methods for calculating outcomes were valid.

Definition of Ratings Based on Above Criteria

Good: Relevant and adequately described study populations for the outcome of interest (i.e., Sensitivity, Specificity), screening test well described in terms of test procedures followed and threshold used for a "positive" or "negative" test, credible reference standard used for outcome of interest (i.e., Sensitivity or Specificity), generally interprets reference standard independently of screening test, outcomes clearly reported and valid, handles indeterminate results in a reasonable manner.

Fair: Mostly includes a relevant and adequately described study population for the outcome of interest (i.e., Sensitivity, Specificity), screening test described although may include some ambiguity about test procedures followed or threshold for a "positive" or "negative" test, credible reference standard mostly used for outcome of interest (i.e., Sensitivity or specificity), interpretation of reference standard may or may not be independent of screening test, outcomes mostly clearly reported although may have some ambiguity regarding how indeterminate results were handled.

Poor: Has fatal flaw such as study population not appropriate for outcome of interest (i.e., Sensitivity, Specificity), screening test improperly administered or not at all described, use of noncredible reference standard, reference and screening test not independently assessed, outcomes not clearly or accurately reported with no information about how indeterminate tests were handled.

Criteria Adapted from: U.S. Preventive Services Task Force, Procedure Manual Appendix VII http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual---appendix-vii, Harris et al., 2001[31]

Appendix C. Excluded Studies

X1. Not original research
X2. Ineligible Population
X3. Ineligible or No Screening/Intervention(s)
X4. Ineligible or No Comparator(s)
X5. Ineligible or No Outcome(s)
X6. Ineligible Setting
X7. Ineligible Study Design
X8. Could Not Obtain Full Text
X9. Poor Quality

1. Sharma SK, Sharma A, Kadhiravan T, et al. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database Syst Rev. 2013;7:Cd007545. PMID: 23828580. Exclusion Code: X7
2. Longhi RM, Zembrzuski VM, Basta PC, et al. Genetic polymorphism and immune response to tuberculosis in indigenous populations: a brief review. Braz J Infect Dis. 2013 May-Jun;17(3):363-8. PMID: 23665009. Exclusion Code: X3
3. Cohen D, Corbett E. Evidence supports TB test, so what now? Cochrane Database Syst Rev. 2013;2:Ed000051. PMID: 23450616. Exclusion Code: X1
4. Steingart KR, Sohn H, Schiller I, et al. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2013;1:Cd009593. PMID: 23440842. Exclusion Code: X3
5. Munoz L, Santin M. Interferon-gamma release assays versus tuberculin skin test for targeting people for tuberculosis preventive treatment: an evidence-based review. J Infect. 2013 Apr;66(4):381-7. PMID: 23298892. Exclusion Code: X5
6. Horne DJ, Pinto LM, Arentz M, et al. Diagnostic accuracy and reproducibility of WHO-endorsed phenotypic drug susceptibility testing methods for first-line and second-line antituberculosis drugs. J Clin Microbiol. 2013 Feb;51(2):393-401. PMID: 23152548. Exclusion Code: X3
7. Rogerson TE, Chen S, Kok J, et al. Tests for latent tuberculosis in people with ESRD: a systematic review. Am J Kidney Dis. 2013 Jan;61(1):33-43. PMID: 23068425. Exclusion Code: X5
8. Dai Y, Feng Y, Xu R, et al. Evaluation of interferon-gamma release assays for the diagnosis of tuberculosis: an updated meta-analysis. Eur J Clin Microbiol Infect Dis. 2012 Nov;31(11):3127-37. PMID: 22833244. Exclusion Code: X2
9. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-gamma release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest. 2012 Jul;142(1):63-75. PMID: 22490872. Exclusion Code: X2
10. Fan L, Chen Z, Hao XH, et al. Interferon-gamma release assays for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. FEMS Immunol Med Microbiol. 2012 Aug;65(3):456-66. PMID: 22487051. Exclusion Code: X2
11. Chang K, Lu W, Wang J, et al. Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: a meta-analysis. J Infect. 2012 Jun;64(6):580-8. PMID: 22381459. Exclusion Code: X3
12. Shahidi N, Fu YT, Qian H, et al. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis. 2012 Nov;18(11):2034-42. PMID: 22294550. Exclusion Code: X2
13. Fenner L, Rieder HL. Isoniazid preventive therapy for all: are we ready? Int J Tuberc Lung Dis. 2011 Oct;15(10):1281-2. PMID: 22283884. Exclusion Code: X1
14. Amerio P, Amoruso G, Bardazzi F, et al. Detection and management of latent tuberculosis infections before biologic therapy for psoriasis. J Dermatolog Treat. 2013 Aug;24(4):305-11. PMID: 22208431. Exclusion Code: X1
15. Nienhaus A, Schablon A, Costa JT, et al. Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC Health Serv Res. 2011;11:247. PMID: 21961888. Exclusion Code: X5
16. Mrozek N, Pereira B, Soubrier M, et al. Screening of tuberculosis before biologics. Med Mal Infect. 2012 Jan;42(1):1-4. PMID: 21907513. Exclusion Code: X7
17. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet

Infect Dis. 2012 Jan;12(1):45-55. PMID: 21846592. Exclusion Code: X5
18. Zhou Q, Chen YQ, Qin SM, et al. Diagnostic accuracy of T-cell interferon-gamma release assays in tuberculous pleurisy: a meta-analysis. Respirology. 2011 Apr;16(3):473-80. PMID: 21299686. Exclusion Code: X4
19. Zwerling A, van den Hof S, Scholten J, et al. Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. Thorax. 2012 Jan;67(1):62-70. PMID: 21228420. Exclusion Code: X2
20. Diel R, Goletti D, Ferrara G, et al. Interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. Eur Respir J. 2011 Jan;37(1):88-99. PMID: 21030451. Exclusion Code: X2
21. Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. Int J Tuberc Lung Dis. 2010 Nov;14(11):1374-81. PMID: 20937175. Exclusion Code: X7
22. Erkens CG, Kamphorst M, Abubakar I, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. Eur Respir J. 2010 Oct;36(4):925-49. PMID: 20889463. Exclusion Code: X1
23. Freeman RJ, Mancuso JD, Riddle MS, et al. Systematic review and meta-analysis of TST conversion risk in deployed military and long-term civilian travelers. J Travel Med. 2010 Jul-Aug;17(4):233-42. PMID: 20636596. Exclusion Code: X2
24. Greenaway C, Sandoe A, Vissandjee B, et al. Tuberculosis: evidence review for newly arriving immigrants and refugees. Cmaj. 2011 Sep 6;183(12):E939-51. PMID: 20634392. Exclusion Code: X7
25. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25. PMID: 20577159. Exclusion Code: X1
26. Chang KC, Leung CC. Systematic review of interferon-gamma release assays in tuberculosis: focus on likelihood ratios. Thorax. 2010 Mar;65(3):271-6. PMID: 20335301. Exclusion Code: X2
27. Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. Chest. 2010 Apr;137(4):952-68. PMID: 20022968. Exclusion Code: X2
28. Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clin Infect Dis. 2009 Dec 15;49(12):1883-9. PMID: 19911936. Exclusion Code: X7
29. Bliven EE, Podewils LJ. The role of chronic hepatitis in isoniazid hepatotoxicity during treatment for latent tuberculosis infection. Int J Tuberc Lung Dis. 2009 Sep;13(9):1054-60. PMID: 19723392. Exclusion Code: X7
30. Sadatsafavi M, Shahidi N, Marra F, et al. A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy. J Clin Epidemiol. 2010 Mar;63(3):257-69. PMID: 19692208. Exclusion Code: X5
31. Pai M, Ramsay A, O'Brien R. Evidence-based tuberculosis diagnosis. PLoS Med. 2008 Jul 22;5(7):e156. PMID: 18651788. Exclusion Code: X1
32. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med. 2008 Aug 5;149(3):177-84. PMID: 18593687. Exclusion Code: X2
33. Madariaga MG, Jalali Z, Swindells S. Clinical utility of interferon gamma assay in the diagnosis of tuberculosis. J Am Board Fam Med. 2007 Nov-Dec;20(6):540-7. PMID: 17954861. Exclusion Code: X7
34. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med. 2007 Mar 6;146(5):340-54. PMID: 17339619. Exclusion Code: X2
35. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess. 2007 Jan;11(3):1-196. PMID: 17266837. Exclusion Code: X3
36. Farhat M, Greenaway C, Pai M, et al. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis. 2006 Nov;10(11):1192-204. PMID: 17131776. Exclusion Code: X2
37. Gao XF, Wang L, Liu GJ, et al. Rifampicin plus pyrazinamide versus isoniazid for treating latent tuberculosis infection: a meta-analysis. Int J Tuberc Lung Dis. 2006 Oct;10(10):1080-90. PMID: 17044199. Exclusion Code: X7

38. Balcells ME, Thomas SL, Godfrey-Faussett P, et al. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006 May;12(5):744-51. PMID: 16704830. Exclusion Code: X2
39. Fraser A, Paul M, Attamna A, et al. Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. Int J Tuberc Lung Dis. 2006 Jan;10(1):19-23. PMID: 16466032. Exclusion Code: X2
40. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clin Infect Dis. 2005 Mar 1;40(5):670-6. PMID: 15714411. Exclusion Code: X4
41. Pai M, Riley LW, Colford JM, Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. Lancet Infect Dis. 2004 Dec;4(12):761-76. PMID: 15567126. Exclusion Code: X2
42. Smieja MJ, Marchetti CA, Cook DJ, et al. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev. 2000(2):Cd001363. PMID: 10796642. Exclusion Code: X7
43. Temple ME, Nahata MC. Rifapentine: its role in the treatment of tuberculosis. Ann Pharmacother. 1999 Nov;33(11):1203-10. PMID: 10573321. Exclusion Code: X2
44. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. Chest. 1991 Feb;99(2):465-71. PMID: 1824929. Exclusion Code: X7
45. O'Shea MK, Fletcher TE, Tupper D, et al. Screening for latent tuberculosis and gastrointestinal parasite infections in Gurkha recruits: research driving policy change. J R Army Med Corps. 2014 Jun;160(2):180-2. PMID: 24607484. Exclusion Code: X2
46. Ang M, Wong WL, Kiew SY, et al. Prospective head-to-head study comparing 2 commercial interferon gamma release assays for the diagnosis of tuberculous uveitis. Am J Ophthalmol. 2014 Jun;157(6):1306-14; 14.e1-4. PMID: 24508163. Exclusion Code: X2
47. Auld SC, Click ES, Heilig CM, et al. Tuberculin skin test result and risk of death among persons with active TB. PLoS One. 2013;8(11):e78779. PMID: 24244358. Exclusion Code: X5
48. Auld SC, Click ES, Heilig CM, et al. Association between tuberculin skin test result and clinical presentation of tuberculosis disease. BMC Infect Dis. 2013;13:460. PMID: 24093965. Exclusion Code: X2
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Appendix D Table 1. Studies of Sensitivity of TST Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	TST 5-mm Sensitivity (95% CI, Interval) (N)	TST 10-mm Sensitivity (95% CI, Interval) (N)	TST 15-mm Sensitivity (95% CI, Interval) (N)	Quality Rating
Ak, 2009[70]	Turkey (I)	47.7[b]	34.4[b] (17.9)	0	100.0	Data extracted for subjects with culture confirmation. Testing completed before treatment started for 90% of participants, and within 7 days of starting treatment for the remainder.		0.61 (0.45 to 0.75) (36)		Good
Berkel, 2005[54]	Netherlands (L)	NR	NR	0	39.0[b]	Data extracted for culture-confirmed patients; 19% were immunocompromised. Among sample, 86% were older than 45 years of age. BCG status reported for portion of study group. No information available on timing of testing with respect to treatment.	0.99 (0.97 to 1.00) (312)	0.96 (0.93 to 0.97) (312)	0.80 (0.75 to 0.84) 312	Fair
Bocchino, 2010[74]	Italy (L)	60.0	39.2 (14.3)	0	43.3	Data extracted for subjects tested at baseline with culture confirmation or positive AFB smear. Study excluded subjects receiving previous TB treatment.	0.75 (0.63 to 0.84) (60)			Fair
Dilektasli, 2010[75]	Turkey (I)	NR[b]	36.7[b] (13.7)	NR	84.0	Data extracted for subjects with culture confirmation who had received treatment for less than 4 weeks.	0.87 (0.71 to 0.95) (31)	0.84 (0.67 to 0.93) (31)	0.26 (0.14 to 0.43) (31)	Fair
Fietta, 2003[53]	Italy (L)	73.7	48.5 (NR)	0	NR	Study subjects had culture confirmation. Testing completed prior to treatment initiation.	0.65 (0.52 to 0.76) (57)			Fair
Kang, 2005[55]	South Korea (I)	59.0	Median: 43 Range: 17 to 84	0	56.0	Study subjects had pathologic or culture confirmation. Demographic data exclude indeterminates. No information available on timing of testing with respect to treatment.		0.78 (0.65 to 0.87) (54)	0.70 (0.57 to 0.81) (54)	Fair
Mazurek, 2007[62]	United States (L)	56.8[b]	46.6[b] Median: 46.4 Range: 16 to 87.1	0	33.8[b]	Data extracted for subjects with mycobacterial confirmation and known negative HIV status. Subjects receiving treatment for longer than 7 days were not included.	0.74 (0.62 to 0.83) (69)	0.71 (0.59 to 0.80) (69)	0.62 (0.51 to 0.73) (69)	Good
Painter, 2013[51]	Vietnam (H)	68.9[b]	37.3[b] Range: 15 to 65 and older	0.1[b]	100.0	Data extracted for subjects with culture confirmation. No information available on timing of testing with respect to treatment.	0.89 (0.83 to 0.94) (132)	0.81 (0.74 to 0.87) (132)	0.52 (0.44 to 0.61) (132)	Fair
Park, 2009[73]	South Korea (I)	54.0	52.2 (16.5)	0	NR	Data extracted for subjects with culture confirmation. No information available on timing of testing with respect to treatment.		0.76 (0.68 to 0.82) (153)		Fair

Appendix D Table 1. Studies of Sensitivity of TST Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	TST 5-mm Sensitivity (95% CI, Interval) (N)	TST 10-mm Sensitivity (95% CI, Interval) (N)	TST 15-mm Sensitivity (95% CI, Interval) (N)	Quality Rating
Seibert, 1991[52]	United States (L)	67.0[b]	47[b] (18.4)	NR	NR	Data extracted for subjects with extrapulmonary TB culture-confirmed from sputum, pleural fluid, or pleural biopsy with demonstrated clinical evidence for TB. No information available on timing of testing with respect to treatment.		0.93 (0.81 to 0.98) (43)		Fair
Soysal, 2008[69]	Turkey (I)	56.0	35 (16)	0	78.0	Data extracted for subjects with culture confirmation. All subjects had been untreated or treated for less than 7 days at the time of testing.	0.81 (0.72 to 0.87) (99)	0.70 (0.60 to 0.78) (99)	0.41 (0.32 to 0.51) (99)	Fair
Tsiouris, 2006[57]	South Africa (H)	62.3[b]	Male[b]: 38 Female: 36.5 (NR)	0	65.7[b]	Study subjects had culture confirmation. Data extracted for HIV-negative subjects.		0.94 (0.72 to 0.99) (16)		Good
Wlodarczyk, 2014[98]	Poland (I)	51.2	48.6 (18.2)	0	100	Data extracted for subjects with culture confirmation. Timing of treatment in relation to testing unstated.	0.58 (0.43 to 0.72) (43)	0.56 (0.41 to 0.70) (43)	0.26 (0.15 to 0.40) (43)	Good

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.

Abbreviations: AFB=acid fast bacilli; BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 2. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Adetifa, 2007[58]	Gambia (H)	63.8	31.2 IQR: 23 to 36	8.8	23.8	Data extracted for subjects with smear and culture confirmation. No information available on timing of testing with respect to treatment.			0.64 (0.53 to 0.74) (75)	Fair
Ak, 2009[70]	Turkey (I)	47.7[b]	34.4[b] (17.9)	0	100.0	Data extracted for subjects with culture confirmation. Testing completed before treatment started for 90% of participants, and within 7 days of starting treatment for the remainder.		0.78 (0.62 to 0.88) (36)		Good
Bocchino, 2010[74]	Italy (L)	60.0	39.2 (14.3)	0	43.3	Data extracted for subjects tested at baseline with culture confirmation or positive AFB smear. Study excluded subjects receiving previous TB treatment.			0.88 (0.78 to 0.94) (60)	Fair
Boyd, 2011[79]	United Kingdom (I)	57.0[b]	NR	7.0[b]	NR	Data extracted for subjects with positive AFB sputum, culture, or molecular confirmation. No information available on timing of testing with respect to treatment.	0.76 (0.59 to 0.87) (33)			Good
Chee, 2008[64]	Singapore (I)	74.1	Median: 48.6 Range: 17 to 77	0	NR	Data extracted for HIV-negative subjects with culture confirmation. Study population recruited up to 14 days after starting treatment but 79% tested within 7 days of receiving treatment.	0.94 (0.90 to 0.96) (263)		0.79 (0.74 to 0.83) (283)	Good
Cho, 2011[80]	South Korea (I)	41.1[b]	48.3[b] (16.1)	0	NR	Data extracted for immunocompetent subjects with culture or PCR confirmation. No information available on timing of testing with respect to treatment.	0.88 (0.80 to 0.92) (120)			Good
Dewan, 2007[59]	United States (L)	NR	Range[b]: 0 to 76	9.0[b]	NR	Data extracted for group including three HIV-positive subjects.		0.62 (0.46 to 0.76) (37)		Fair
Dilektasli, 2010[75]	Turkey (I)	36.7[b]	13.4[b] (NR)	NR	84.0	Data extracted for subjects with culture confirmation who had received treatment for less than 4 weeks.	0.74 (0.57 to 0.86) (31)			Fair

Appendix D Table 2. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Erdem, 2014[99]	Multiple (L and I)	52.6	39.7 (18.4)	NR	NR	Patient population culture confirmed tuberculous meningitis. Timing of test with respect to treatment not reported.			0.90 (0.77 to 0.96) (41)	Fair
Feng, 2013[91]	Taiwan (I)	67.5	63.6 (19.7)	0	47.6	Data extracted for subjects with pathology or culture confirmation. Timing of testing with respect to treatment unclear.			0.88 (0.81 to 0.92) (130)	Fair
Goletti, 2006[56]	Italy(L)	65.2	33 (SE ± 2)	0	78.3	Study subjects had positive AFB smear or culture confirmation. Testing completed before treatment initiation.	0.91 (0.73 to 0.98) (23)	0.83 (0.63 to 0.93) (23)		Fair
Harada, 2008[65]	Japan (I)	73.0	53.3 (NR)	1.0	37.0	Study subjects had positive culture or positive nucleic acid amplification. All subjects received less than 7 days of treatment prior to testing.		0.79 (0.70 to 0.86) (100)	0.87 (0.79 to 0.92) (100)	Good
Higuchi, 2009[71]	Japan (I)	78.7	52.7 Range: 17 to 91	NR	100.0	Study subjects had culture, PCR, or positive smear confirmation before treatment or within 1 week after the start of treatment.	0.96 (0.86 to 0.99) (49)	0.87 (0.75 to 0.94) (47)		Fair
Janssens, 2007[60]	Switzerland (L)	51.7	37 (17)	0	NR	Study subjects had smear or culture confirmation. Foreign-born represented 86% of the study group. Testing completed within 2 weeks of initiating treatment.	0.98 (0.91 to 1.00) (58)			Fair
Jeon, 2013[92]	South Korea (I)	60.7	54.8 (20.1)	0	NR	Data extracted for subjects with PCR or culture confirmation. In this group, 13.7% were non-HIV immunosuppressed due to medications or advanced cancer. Subjects taking TB medication prior to exam were excluded.			0.65 (0.57 to 0.72) (168)	Fair
Kang, 2005[55]	South Korea (I)	59.0	Median: 43 Range: 17 to 84	0	56.0	Study subjects had pathologic or culture confirmation. Demographic data excludes indeterminates. No information available on timing of testing with respect to treatment.		0.76 (0.63 to 0.85) (58)		Fair

Appendix D Table 2. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Kim, 2011[81]	South Korea (I)	54.4	Median: 49 Range: 16 to 94	0	NR	Data extracted for subjects with culture confirmation. QFT testing completed before treatment initiation.			0.86 (0.82 to 0.89) (362)	Good (QFT-G) Poor (TST)
Kim, 2013[93]	South Korea (I)	56.5	Median: 48 Range: 28 to 86	NR	67.4	Data extracted for subjects with positive sputum culture or molecular confirmation, though 2 subjects had clinical confirmation. No information available on the timing of testing with respect to treatment.			0.89 (0.77 to 0.95) (46)	Fair
Kim, 2014[100]	South Korea (I)	39.0	64.0 (19)	5.0	NR	Study population limited to those with military TB. Timing of testing with respect to treatment not specifically reported, but testing was done within 5 days of hospital presentation, so likely no treatment for longer than 7 days prior to testing.			0.68 (0.53 to 0.80) (44)	Good
Kobashi, 2008[66]	Japan (I)	64.3	62.8 (10.8)	0	NR	Study subjects had microbiologic confirmation. No information on timing of testing with respect to treatment available, although study excluded 10 patients due to previous TB treatment.		0.81 (0.68 to 0.90) (48)		Fair
Kobashi, 2008[68]	Japan (I)	77.0	NR	0	60.8	Study subjects had culture-confirmed pulmonary or extrapulmonary TB. No information available on the timing of testing with respect to treatment.		0.81 (0.68 to 0.90) (48)		Fair
Kobashi, 2008[67]	Japan (I)	75.0	59.6 (10.6)	0	58.0	Data extracted for subjects with culture confirmation. Testing completed prior to treatment initiation.	0.88 (0.75 to 0.94) (48)	0.85 (0.77 to 0.90) (130)		Good
Kobashi, 2009[72]	Japan (I)	60.0	57.7 (10.2)	1.0	60.1	Data extracted for subjects with culture confirmation. No information available on the timing of testing with respect to treatment.		0.81 (0.68 to 0.90) (48)		Fair

Appendix D Table 2. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Kobashi, 2012[88]	Japan (I)	77.2	65.2 (10)	0	NR	Study subjects had culture-confirmed pulmonary or extrapulmonary TB. 9% of subjects received previous anti-TB treatment and 14% of subjects received immunosuppressive treatment. No information available on the timing of testing with respect to treatment.	0.95 (0.78 to 0.99) (22)	0.82 (0.61 to 0.93) (22)	0.86 (0.67 to 0.95) (22)	Fair
Lai, 2011[83]	Taiwan (I)	71.0[b]	57.5[b] (18.5)	8.0[b]	NR	Data extracted for subjects with culture confirmation. No information available on timing of testing with respect to treatment.	0.90 (0.60 to 0.98) (10)		0.65 (0.55 to 0.74) (98)	Fair
Lai, 2011[82]	Taiwan (I)	51.1[b]	55.2[b] (16.4)	6.7[b]	NR	Data extracted for subjects with M.Tb culture confirmation. No information available on timing of testing with respect to treatment.	0.88 (0.80 to 0.93) (98)			Fair
Lee, 2012[89]	South Korea (I)	62.0	61 (19.4)	0	NR	Study subjects had positive nucleic acid amplification PCR or culture confirmation from sputum or pleural fluid. No information available on timing of testing with respect to treatment.			0.78 (0.67 to 0.87) (65)	Good
Legesse, 2010[76]	Ethiopia (H)	54.3[b]	34.2[b] (NR)	0	20.0[b]	Data extracted for subjects with culture confirmation or positive AFB smear. Study excluded patients on TB treatment.			0.65 (0.47 to 0.79) (31)	Fair
Losi, 2007[61]	Netherlands, Germany, and Italy (L)	40.0	42.3 (17.4)	NR	NR	Data extracted for subjects with microbiological or PCR confirmation. No information available on timing of test with respect to treatment.	1.00 (0.72 to 1.00) (10)			Fair
Lui, 2011[84]	Hong Kong (I)	74.6	Median: 47	1.6	83.0	Data extracted for subjects with culture or histologic confirmation, with 3 patients confirmed by clinic-radiologic characteristics and response to therapy. Testing performed prior to initiation of treatment.		0.60 (0.47 to 0.72) (55)		Fair

Appendix D Table 2. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Metcalfe, 2010[77]	United States (L)	69.0	Median: 50 IQR: 36 to 62	0	18.0	Study subjects had culture confirmed pulmonary or extrapulmonary TB but were AFB smear-negative. Study excluded patients who had received TB treatment for 7 days or longer.		0.72 (0.60 to 0.82) (65)		Fair
Min, 2013[94]	South Korea (I)	56.8[b]	Median[b]: 66 Range: 27 to 90	NR	32.4[b]	Data extracted for subjects with culture confirmation. 7 subjects had history of treatment although no information available on the timing of treatment with respect to testing.			0.85 (0.68 to 0.94) (27)	Fair (Sn) Poor (Sp)
Pai, 2007[63]	India (H)	75.0[b]	36.4[b] Range: 18 to 76	0	41.0[b]	Data extracted for HIV-negative subjects with culture or smear confirmation. Data extracted only from testing before treatment.			0.76 (0.60 to 0.87) (37)	Good
Painter, 2013[51]	Vietnam (H)	68.9[b]	37.3[b] Range: 15 to 65 and older	0.1[b]	100.0	Data extracted for subjects with culture confirmation. No information available on timing of testing with respect to treatment.			0.86 (0.79 to 0.91) (132)	Fair
Park, 2009[73]	South Korea (I)	54.0	52.2 (16.5)	0	NR	Data extracted for subjects with culture confirmation. No information available on timing of testing with respect to treatment.			0.88 (0.82 to 0.92) (153)	Fair
Qian, 2013[95]	China (H)	66.2[b]	45.8 (17.3)[b]	0	84.7[b]	Data extracted for subjects with positive AFB smear. No subjects were receiving treatment.			0.82 (0.75 to 0.87) (157)	Fair
Ra, 2011[85]	South Korea (I)	42.1	Median: 49 Range: 22 to 83	0	84.6	Data extracted for subjects with positive AFB smear and culture confirmation. Information not available on timing of testing with respect to treatment. Subjects included 9 patients with prior history of TB and 13 immunosuppressed patients.		0.89 (0.76 to 0.96) (38)		Fair (QFT-G) Poor (TST)
Ruhwald, 2011[86]	Italy (L), Denmark (L), Sweden (L), Spain (I), Greece (L), Finland (L)	57.0	Median: 37 Range: 18 to 90	7.0	NR	Study subjects had positive culture, PCR, or microscopy or histology with a response to treatment. Testing completed within the first 2 weeks of treatment.	0.90 (0.78 to 0.95) (48)		0.79 (0.72 to 0.85) (168)	Good

Appendix D Table 2. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Soysal, 2008[69]	Turkey (I)	56.0	35 (16)	0	78.0	Data extracted for subjects with culture confirmation. All subjects had been untreated or treated for less than 7 days at the time of testing.	0.83 (0.75 to 0.89) (96)	0.78 (0.69 to 0.85) (100)		Fair
Taki-Eddin, 2012[90]	Syria (I)	NR	NR	NR	NR	Data extracted for subjects with culture confirmation. No information available on timing of testing with respect to treatment.			0.87 (0.73 to 0.94) (38)	Fair
Tan, 2010[78]	Taiwan (I)	75.0[b]	67[b] (12.9)	1.2[b]	NR	Data extracted for subjects with culture confirmation. All subjects had diabetes. 5 subjects were reported to have received anti-TB treatment prior to testing, but timing of treatment is not described.	0.86 (0.72 to 0.93) (42)			Fair
Tsiouris, 2006[57]	South Africa (H)	62.3[b]	Male:[b] 38 Female: 36.5 (NR)	0	65.7[b]	Study subjects had culture confirmation. Data extracted for HIV-negative subjects.			0.73 (0.48 to 0.89) (15)	Good
Walsh, 2011[87]	United States (L), Mexico (I)	65.1 67.5	Range: 20 to 60 and older Range: 20 to 60 and older	7.0 3.0	87.5 74.5	Study excluded patients receiving treatment more than 7 days with culture confirmation or AFB smear positive.	0.93 (0.81 to 0.98) (43)	0.70 (0.63 to 0.77) (169)		Fair
Wang, 2013[96]	China (H)	65.4	46 Range: 20 to 75	0	80.1	Data extracted for subjects with positive AFB smear or sputum culture confirmation. Subjects received testing prior to or within 7 days of beginning treatment.			0.85 (0.66 to 0.94) (26)	Fair
Wlodarczyk, 2014[98]	Poland (I)	51.2	48.6 (18.2)	0	100	Data extracted for subjects with culture confirmation. Timing of treatment in relation to testing unstated.			0.65 (0.50 to 0.78) (43)	Good

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.

Abbreviations: AFB=acid fast bacilli; BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; IQR=interquartile range; M.Tb=*Mycobacterium tuberculosis*; N=number analyzed; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 3. Studies of Specificity of TST Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	TST 5-mm Specificity (95% CI, Interval) (N)	TST 10-mm Specificity (95% CI, Interval) (N)	TST 15-mm Specificity (95% CI, Interval) (N)	Quality Rating
Bellete, 2002[116]	United States (L)	41.1[b]	NR	NR	NR	Data extracted for study subjects at low risk for TB.			0.96 (0.87 to 0.99) (52)	Fair
Berkel, 2005[54]	Netherlands (L)	41.0	24.2 (6.1)	NR	0	Study only included patients under 40 years of age and excluded patients with BCG vaccination. All study subjects screened due to intended travel.	0.95 (0.94 to 0.96) (2848)	0.97 (0.96 to 0.98) (2848)	0.99 (0.98 to 0.99) (2848)	Fair
Bienek, 2009[121]	United States (L)	83.5[b]	NR	0	3.3[b]	Data extracted for participants classified as "low risk" for TB.		1.00 (0.99 to 1.00) (296)		Fair
Dilektasli, 2010[75]	Turkey (I)	36.7[b]	13.7[b] (NR)	NR	93.4[b]	Study subjects were healthy controls with no history of TB or exposure.			0.57 (0.39 to 0.73) (30)	Fair
Fietta, 2003[53]	Italy (L)	57.1	27 (NR)	0	0	Study subjects were healthy, "low-risk" volunteers with no stated possible risk factors for M.tb exposure.		0.95 (0.84 to 0.99) (42)		Fair
Katsenos, 2010[122]	Greece (L)	100.0	24.3 (4.0)	NR	100.0	Population is Greek army recruits. Study excluded individuals with treatment for active or latent TB, suspected current TB, prior "severe" TST reaction, known TB exposure, or any known immunosuppressive condition.	0.94 (0.92 to 0.95) (1750)	0.95 (0.93 to 0.95) (1750)	0.97 (0.96 to 0.97) (1750)	Good
Mancuso, 2012[123]	United States (L)	65.5[b]	21.8[b] (4.6)	NR	3.5[b]	Data extracted for subjects classified as "low risk" for TB based on history. Population is U.S. military recruits.		0.99 (0.98 to 0.99) (1373)	0.99 (0.99 to 1.00) (1373)	Fair
Mazurek, 2001[115]	United States (L)	50.0[b]	39[b] (NR)	0	NR	Data extracted for subjects at low risk for latent TB.			0.98 (0.93 to 0.99) (98)	Good
Mazurek, 2007[120]	United States (L)	94.3[b]	20[b] Median: 20 Range: 17 to 39	NR	2.2	Data extracted for subjects classified as "low risk" for TB. Population is U.S. Navy recruits.	0.97 (0.95 to 0.98 (551)	0.98 (0.97 to 0.99) (551)	0.99 (0.98 to 1.00) (551)	Fair
Soysal, 2008[69]	Turkey (I)	62.0	22 (12)	0	83.0	Population is healthy medical students with no previous clinical patient contact and no history of TB exposure.	0.30 (0.19 to 0.44) (47)	0.45 (0.31 to 0.59) (47)	0.60 (0.45 to 0.72) (47)	Fair

Appendix D Table 3. Studies of Specificity of TST Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	TST 5-mm Specificity (95% CI, Interval) (N)	TST 10-mm Specificity (95% CI, Interval) (N)	TST 15-mm Specificity (95% CI, Interval) (N)	Quality Rating
Taggart, 2004[117]	United States (L)	50.0[b]	31.5 (NR)	0	0				0.92 (0.83 to 0.97) (66)	Fair
Taggart, 2006[118]	United States (L)	42.3[b]	37.3 Range: 20 to 67	NR	0	Data extracted for subjects considered low risk with no known risk factors for TB exposure, non-BCG vaccinated, with no history of active TB infection. Study subjects enrolled at an on-site employee health clinic. Participants originated from 20 countries.			0.96 (0.90 to 0.99) (81)	Fair
Villarino, 1999[113]	United States (L)	38.0	Median: 26 Range: 18 to 50	NR	0	Participants received the TST with the PPD-S1 antigen. Study excluded any person with known immunodeficiency.		0.99 (0.98 to 0.99) (1555)	1.00 (0.99 to 1.00) (1555)	Fair
Villarino, 2000[114]	United States (L)	37.8	Median: 27	NR	0	Participants received the TST with the PPD-S2 antigen. Study excluded any person known to have a condition that could suppress delayed-type hypersensitivity, including HIV infection.		0.98 (0.98 to 0.99) (1189)	1.00 (0.99 to 1.00) (1189)	Fair

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number analyzed; NR=not reported; M.Tb=*Mycobacterium tuberculosis*; PPD=purified protein derivative; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 4. Studies of Specificity of IGRA Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Specificity (95% CI, Interval) (N)	QFT-G Specificity (95% CI, Interval) (N)	QFT-GIT Specificity (95% CI, Interval) (N)	Quality Rating
Bienek, 2009[121]	United States (L)	83.5[b]	NR	0	3.3[b]	Data extracted for participants classified as "low risk" for TB.	0.95 (0.91 to 0.97) (291)			Fair
Bua, 2007[119]	Italy (L)	51.9	Median: 45 Range: 20 to 70	NR	NR	Data extracted for healthy subjects with negative TST.		1.00 (0.81 to 1.00) (16)		Fair
Dilektasli, 2010[75]	Turkey (I)	36.7[b]	13.7[b] (NR)	NR	93.4[b]	Study subjects were healthy controls with no history of TB or exposure.	0.73 (0.56 to 0.86) (30)			Fair
Kim, 2013[93]	South Korea (I)	43.8	Median: 37 Range: 18 to 56	NR	78.1	Data extracted for healthy subjects with no known history of contact with TB patients, normal chest radiographs, and no symptoms of active TB.			0.60 (0.49 to 0.71) (73)	Fair
Lempp, 2015[124]	United States (L)	NR	NR	NR	NR	TST, QFT, and QFT-G results from a portion of subjects previously reported; only abstracted data for QFT-GIT low-risk subjects.			0.98 (0.97 to 0.99) (525)	Fair
Mancuso, 2012[123]	United States (L)	65.5[b]	21.8[b] (4.6)	NR	3.5[b]	Data extracted for subjects classified as "low risk" for TB based on history. Population is U.S. military recruits.	0.97 (0.96 to 0.98) (1373)		0.99 (0.98 to 0.99) (1354)	Fair
Ruhwald, 2011[86]	Italy (L), Denmark (L), Spain (I)	59.0[b]	Median: 22 Range: 19 to 53	1.0[b]	NR	Data extracted for subjects with no known exposure to TB and no prior TB diagnosis or treatment. Study subjects were students and nonexposed volunteers.	0.99 (0.92 to 1.00) (70)		0.99 (0.95 to 1.00) (101)	Good
Soysal, 2008[69]	Turkey (I)	62.0	22 (12)	0	83.0	Population was healthy medical students with no previous clinical patient contact and no history of TB exposure.	0.85 (0.72 to 0.92) (46)	0.89 (0.77 to 0.95) (47)		Fair
Taggart, 2006[118]	United States (L)	42.3[b]	37.3 Range: 20 to 67	NR	0	Data extracted for subjects considered low risk with no known risk factors for TB exposure, non-BCG vaccinated, with no history of active TB infection. Study subjects enrolled at an on-site employee health clinic. Participants originated from 20 countries.		1.00 (0.95 to 1.00) (81)		Fair

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 5. Studies of Sensitivity of TST Screening Tests for Tuberculosis (KQ 2), Sensitivity Analysis

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	TST 5-mm Sensitivity (95% CI, Interval) (N)	TST 10-mm Sensitivity (95% CI, Interval) (N)	TST 15-mm Sensitivity (95% CI, Interval) (N)	Quality Rating
Kang, 2007[102]	South Korea (I)	62.5[b]	Median: 55[b] Range: 16 to 81	0	36.1[b]	Data extracted for subjects with culture confirmation. 20% of study population had risk factor for immunosuppression. No information available on timing of testing with respect to treatment.		0.67 (0.55 to 0.77) (67)		Poor
Kim, 2011[81]	South Korea (I)	54.4	Median: 49 Range: 16 to 94	0	NR	Data extracted for subjects with culture confirmation. QFT testing completed before treatment initiation.	0.70[c] (0.60 to 0.78) (96)	0.70[c] (0.60 to 0.78) (96)		Poor (TST only)
Li, 2012[110]	China (H)	58.3	46.9 (21.7)	0	33.3	Data extracted for subjects with culture confirmation. Population includes patients who had been treated for 14 days or less.	0.67 (0.50 to 0.80) (36)			Poor
Memish, 2000[101]	Saudi Arabia (I)	43.4[b]	Median: 38[b] Range: 1 to 78	NR	NR	Data extracted for subjects with culture confirmation, positive AFB smear, or presence of caseating granulomas in histologic sections or cytologic smears with no clinical evidence of other infectious or noninfectious diseases. No information available on timing of testing with respect to treatment.		0.83 (0.67 to 0.92) (35)		Poor
Ozekinci, 2007[103]	Turkey (I)	NR	41 Range: 18 to 63	NR	67.4[b]	Data extracted for subjects with smear or culture confirmation. Treatment received up to 2 weeks prior to testing.		0.82[d] (0.64 to 0.92) (28)	0.82[d] (0.64 to 0.92) (28)	Poor
Ra, 2011[85]	South Korea (I)	42.1	Median: 49 Range: 22 to 83	0	84.6	Data extracted for subjects with positive AFB smear and culture confirmation. Information not available on timing of testing with respect to treatment. Subjects included 9 patients with prior history of TB and 13 immunosuppressed patients.		0.71 (0.47 to 0.87) (17)		Poor (TST only)
Shalabi, 2009[108]	Egypt (I)	73.3	31 (11.1)	0	76.7	Data extracted for subjects with positive AFB smear. No information available on timing of testing with respect to treatment.		0.87 (0.70 to 0.95) (30)		Poor

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.
[c] Estimate represents use of both the 5-mm and 10-mm threshold, which varied by clinical status of the individual tested.
[d] Estimate represents use of both the 10-mm and 15-mm threshold, which varied by BCG vaccination status of the individual tested.

Abbreviations: AFB=acid fast bacilli; BCG=bacille Calmette-Guérin; CI=confidence interval; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); HIV=human immunodeficiency virus; SD=standard deviation; Sn=sensitivity; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 6. Studies of Sensitivity of IGRA Screening Tests for Tuberculosis (KQ 2), Sensitivity Analysis

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Sensitivity (95% CI, Interval) (N)	QFT-G Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	Quality Rating
Eum, 2008[104]	South Korea (I)	92.0	43.6 (2.5)	NR	NR	Data extracted for subjects with culture confirmation. All subjects received TB treatment for less than 1 week at the time of testing.			0.76 (0.57 to 0.89) (25)	Poor
Kalantri, 2009[106]	India (H)	76.0	Range: 24 to 45	NR	NR	Data extracted for subjects with positive AFB smear. No information available on timing of testing with respect to treatment.			0.96 (0.90 to 0.98) (100)	Poor
Kamiya, 2013[112]	Japan (L)	Younger age group: 49.2[b] Older age group: 50.0[b]	Younger age group: 54.0[b] Older age group: 78.0[b]	0	NR	Data extracted for subjects with M.tb confirmation from body site samples. No information available on timing of testing with respect to treatment.			0.88 (0.70 to 0.96) (25)	Poor
Kang, 2007[102]	South Korea (I)	62.5[b]	Median: 55[b] Range: 16 to 81	0	36.1[b]	Data extracted for subjects with culture confirmation. 20% of study population had risk factors for immunosuppression. No information available on timing of testing with respect to treatment.	0.88 (0.78 to 0.94) (67)	0.87 (0.76 to 0.93) (67)		Poor
Kobashi, 2009[107]	Japan (I)	NR	NR	NR	NR	Data extracted for subjects with microbiologic confirmation. No information available on timing of testing with respect to treatment.		0.82 (0.75 to 0.88) (140)		Poor
Li, 2012[110]	China (H)	58.3	46.9 (21.7)	0	33.3	Data extracted for subjects with culture confirmation. Population includes patients who had been treated for 14 days or less.	0.89 (0.75 to 0.96) (36)			Poor
Ozekinci, 2007[103]	Turkey (I)	NR	41 Range: 18 to 63	NR	67.4[b]	Data extracted for subjects with smear or culture confirmation. Treatment received up to 2 weeks prior to testing.	0.93 (0.77 to 0.98) (28)			Poor
Palazzo, 2008[105]	Italy (L)	NR	36 (2)	0	NR	Data extracted for subjects with culture confirmation and positive AFB smear. No information available on timing of testing with respect to treatment.		0.50 (0.29 to 0.71) (18)	0.82 (0.59 to 0.94) (17)	Poor
Shrestha, 2011[109]	Nepal (H)	NR	NR	NR	NR	Data extracted for subjects with positive AFB smear. No information available on timing of testing with respect to treatment.	0.90 (0.74 to 0.97) (30)			Poor
Turtle, 2012[111]	England (I)	53.0[b]	36[b] Range: 17 to 78	0	NR	Data extracted for HIV negative subjects with culture confirmation. No information available on timing of testing with respect to treatment.	0.82 (0.52 to 0.95) (11)			Poor

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.

Abbreviations: AFB=acid fast bacilli; BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; M.Tb=*Mycobacterium tuberculosis*; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); N=number; SD=standard deviation; TB=tuberculosis.

Appendix D Table 7. Studies of Specificity of TST Screening Tests for Tuberculosis (KQ 2), Sensitivity Analysis

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	TST 5-mm Specificity (95% CI, Interval) (N)	TST 10-mm Specificity (95% CI, Interval) (N)	TST 15-mm Specificity (95% CI, Interval) (N)	Quality Rating
Franken, 2007[126]	Netherlands (L)	91.8	19.6 (2.8)	NR	8.8	Population is Dutch armed forces recruits. 2 subjects were known to have been treated previously for TB.		0.89 (0.83 to 0.93) (153)	0.92 (0.87 to 0.95) (153)	Poor
Ozekinci, 2007[103]	Turkey (I)	NR	30 Range: 17 to 61	NR	67.4[b]	Data extracted for subjects with no history of exposure to TB.		0.46[c] (0.30 to 0.64) (28)		Poor
Shalabi, 2009[108]	Egypt (I)	58.1	39.4 (12.6)	0	77.4	Data extracted for healthy control subjects.		0.84 (0.67 to 0.93) (31)		Poor

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.
[c] Estimate represents use of both the 10-mm and 15-mm threshold, which varied by BCG vaccination status of the individual tested.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; M.Tb=*Mycobacterium tuberculosis*; NR=not reported; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 8. Studies of Specificity of IGRA Screening Tests for Tuberculosis (KQ 2), Sensitivity Analysis

First Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Specificity (95% CI, Interval) (N)	QFT-G Specificity (95% CI, Interval) (N)	QFT-GIT Specificity (95% CI, Interval) (N)	Quality Rating
Franken, 2007[126]	Netherlands (L)	91.8	19.6 (2.8)	NR	8.8	Population is Dutch armed forces recruits; 2 subjects were known to have been previously treated for TB.			0.97 (0.93 to 0.99) (171)	Poor
Min, 2013[94]	South Korea (I)	57.6	Median: 28 Range: 23 to 42	NR	75.6	Data extracted for health volunteer study subjects with neither a history of TB treatment nor contact with active TB patients.			0.94 (0.80 to 0.98) (33)	Poor (Sp) Fair (Sn)
Ozekinci, 2007[103]	Turkey (I)	NR	30 Range: 17 to 61	NR	67.4[b]	Data extracted for subjects with no history of exposure to TB.	0.89 (0.73 to 0.96) (28)			Poor
Palazzo, 2008[105]	Italy (L)	NR	37 (2)	0	21.0	Data extracted for healthy control subjects.		0.94 (0.72 to 0.99) (16)	1.00 (0.78 to 1.00) (14)	Poor

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; NR=not reported; QFT-G=QuantiFERON-TB Gold (2nd generation test); QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); M.Tb=*Mycobacterium tuberculosis*; SD=standard deviation; Sn=sensitivity; Sp=specificity; TB=tuberculosis.

Appendix D Table 9. Studies of Reliability of Screening Tests for Tuberculosis (KQ 2)

Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Study Population Comments	Test (N)	Reliability Measure	Result	Quality Rating
Cummings 2009[132]	United States (L)	NR	28	NR	7	U.S. HCWs at low risk of TB in a single institution.	QFT-GIT (3-Gen) N=182 N analyzed at 4 weeks=85	Test-retest	2 of 5 positive results on first test were confirmed on subsequent testing At 4 weeks: 85 (47%) of 182 HCWs who had an initial test had the second test; 84 of 85 had consistent results (98.8%)	Poor
Dorman, 2014[127]	United States (L)	25	Median: 36 (IQR: 28 to 48)	0.4	9	U.S. HCWs at 4 U.S. health care institutions	T-SPOT.*TB* and QFT-GIT N=130	Reproducibility Test-retest	Number of discordant results in participants who had 2 samples drawn simultaneously: QFT-GIT: 10/172 (5.8%) T-SPOT.*TB*: 10/153 (6.5%) Test-retest at 2 weeks: T-SPOT.*TB*: 9/111 (8.1%) tests changed from negative to positive and 10/19 (52.6%) changed from positive to negative QFT-GIT: 10/134 (7.5%) results changed from negative to positive and 5/15 (33.3%) changed from positive to negative	Good
Dilektasli 2010[75]	Turkey (I)	36.7	39	NR	90.3	Study included multiple groups, including those with pulmonary TB, close contacts of people with TB, and healthy controls.	T-SPOT.*TB* N=91	Interrater reliability	Interrater reliability[b]=96% (k=0.92; p<0.05) Manual read vs. automated Elispot reader=85.8% (k=0.73; p<0.05)	Fair
Franken, 2009[128]	Netherlands	NR	NR	NR	NR	Immigrants who were close contacts of smear-positive TB patients.	T-SPOT.*TB* N=313	Interrater reliability[b]	Kappas for agreement among 6 raters were all >0.6	Fair
Mancuso, 2012[123]	United States (L)	66	21.8	NR	3.5	U.S. military recruits at low risk of exposure to TB.	TST N=1826	Interrater reliability[b]	Kappa=0.79	Fair
O'Shea, 2014[131]	Nepal (H)	166	NR Range: 18 to 21	0.9	63	Nepalese military recruits who had left Nepal and recently entered the U.K.	T-SPOT.*TB* and QFT-GIT N=166	Test-retest	Test-retest at 1 week: T-SPOT.*TB*: kappa for agreement between initial test and retest: 0.66 (95% CI, 0.50 to 0.83) QFT-GIT: kappa for agreement between initial test and retest: 0.48 (95% CI, 0.26 to 0.7)	Fair
Villarino 2000[114]	United States (L)	37 to 81[c]	50	NR	NR	2 study populations: persons with pulmonary TB and those at low risk of exposure to TB.	TST (PPD S2) N=1189	Interrater reliability[b]	Kappa=0.52 to 0.78 across all groups	Fair

Appendix D Table 9. Studies of Reliability of Screening Tests for Tuberculosis (KQ 2)

Author, Year	Country (TB Burden[a])	% Male	Mean Age in Years (SD)	% HIV	% BCG	Study Population Comments	Test (N)	Reliability Measure	Result	Quality Rating
Villarino 1999[113]	United States (L)	38	26	NR	NR	Persons at low risk for TB.	TST (PPD S1) N=127	Interrater reliability[b]	Kappa=0.69	Fair
Whitworth, 2012[129]	United States (L)	49	NR; all ≥18	NR	28	Subjects with self-reported positive TST recruited from U.S. Air Force and CDC staff located in San Antonio, TX, and Atlanta, GA	QFT-GIT (3-Gen) N=91	Interlaboratory reliability[d]	Across 3 labs, 7/91 (7.7%) subjects had discordant results (none had indeterminate results); kappas of pairwise lab sample comparisons ranged from 0.87, 0.89, and 0.93	Good
Whitworth, 2014[130]	United States (L)	46	NR; all ≥18	NR	21	Subjects with self-reported positive TST recruited from U.S. Air Force and CDC staff located in San Antonio, TX, and Atlanta, GA	QFT-GIT (3-Gen) N=146	Interrater reliability	2 samples from each participant both processed via manual read and automated ELISA; across all 4 tests, 88.6% were concordant (16% concordant positive and 72.6% concordant negative) and 11% were discordant. Discordance by method: Automated vs. automated: 4.8% (kappa=0.85) Manual vs. manual: 6.9% (kappa=0.80) Automated vs. manual: 3.4% to 9.0% across comparisons (kappa=0.73 to 0.90)	Good

[a] TB burden according to World Health Organization classification. (L) Low <10 cases/100,000; (I) Intermediate 10–99 cases/100,000; (H) High >100 cases/100,000.
[b] Agreement between first and second observer.
[c] Among the population with pulmonary TB, 81% were male. Among the population at low risk of exposure to TB, 37% were male.
[d] To measure interlaboratory reliability, three tubes of blood were collected from each subject so that the assay could be completed at three different laboratories noted to have "extensive experience and demonstrated proficiency."

Abbreviations: BCG=bacille Calmette-Guérin; CDC=Centers for Disease Control and Prevention; HIV=human immunodeficiency virus; HCW=health care worker; IQR=intraquartile range; NR=not reported; N=number analyzed; QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); PPD-S1 or S2=purified protein derivative standard 1 or standard 2; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test; U.K.=United Kingdom; U.S.=United States.

Appendix D Table 10. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden[a]	TB Risk Factors	Mean (Range) Age	% F	% Non-white	% BCG	Quality
Menzies, 2004[143] 116	RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months; up to 20 weeks, if needed, depending on missed doses (58). INH 5 mg/kg, up to 300 mg/day x 9 months; up to 43 weeks, if needed, depending on missed doses (58).	16-20 weeks 36-43 weeks Duration of both arms depending on whether treatment was extended due to missed doses.	≥18 years Positive TST following Canadian guidelines; physician recommend 9 INH for LTBI. <5% HIV positive	Yes (TST ≥5-, 10-, and 15-mm, based on risk status under Canadian guidelines). Abnormal CXR: 29 (50) 31 (53)	Canada: low	Contact with active TB case: 10 (17) 10 (17) COB high TB[b]: 45 (78) 48 (83) Randomization stratified by TB risk (high if HIV-infected close contacts with active TB[c], or fibronodular changes CXR; low to moderate for all others).	32.9 (10.8 SD) 34.8 (13.0 SD)	38 50	NR	Yes: 21 Unknown: 19 Yes: 28 Unknown: 21	Fair
Menzies, 2008[133] 847	RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months (420). INH 5 mg/kg, up to 300 mg/day x 9 months (427).	4 months 9 months	18 years or older with a documented positive TST and if physician recommend INH for LTBI following national or international guidelines; 9 university hospitals (7 were in Canada).	Yes	Canada; low[d] Saudi Arabia; intermediate, Brazil; high	HIV infection: 6 (1) 7 (2) Abnormal chest radiograph: 117 (28) 105 (25) Contact with active TB case: 131 (31) 135 (32) Recent immigrant: 29 (7) 33 (8) Of the Canadian participants (who comprised 80% of the sample), born in high TB incidence country: 227 (54) 235 (55)	Age 18-34: 229 (55) 242 (57) Age≥35: 191 (45) 185 (43)	48 47	NR	Yes: 54 47 Unk: 33 25	Good

Appendix D Table 10. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden[a]	TB Risk Factors	Mean (Range) Age	% F	% Non-white	% BCG	Quality
Sterling, 2011[134e] PREVENT TB 6,886	RPT 900 mg + INH 900 mg/week x 12 weeks (3,556) INH 300 mg/day x 36 weeks (3,330)	33 months	≥18 years, TST or IGRA positive excluding HIV-positive patients; close contacts of patients with culture-confirmed TB, recent converters, and small percentage with fibrosis.	Yes[e]	U.S., Canada, Brazil, and Spain; low to high	Close contact within the past 2 years with patient with culture-confirmed TB.	Median: 37[e]	45.8[e]	42.9[e]	NR	Fair
Thompson, 1982[135] IUAT 27,830	INH 300 mg x 12 weeks (6,956). INH 300 mg x 24 weeks (6,965). INH 300 mg x 52 weeks (6,919). Placebo (6,990).	5 years	Age 20-64[f] with fibrotic pulmonary lesions[g] not previously treated with anti-TB meds.	Yes (≥6 mm Mantoux test)[h]	7 European countries[i] low to intermediate	NR	Median: 50 years (NR); 38% were 55 to 65 years	47	NR	NR	Good (for KQ 3) Fair (for KQ 5)
White, 2012[144] 364	RIF 600 mg/day x 4 months; up to 6 months, if needed, depending on missed doses, for a total of 120 doses (180). INH 900 mg 2x week x 9 months; up to 12 months, if needed, depending on missed doses, for a total of 76 doses (184).	16-18 weeks 36-40 weeks Duration of both arms depended on whether treatment was extended due to missed doses, unless necessary to restart (RIF, restart if missed doses >2	Inmates ≥18 years in the San Francisco City and County Jail diagnosed with LTBI at jail entry.	Yes, diagnosis method NR	U.S.: low	Foreign-born: 278 (76); p=0.5 Jailed before: 255 (70); p=0.80 Drug/alcohol problem: 186 (51); p=0.21	<35: 258 (71) ≥35: 106 (29)	7	92	NR	Fair

Appendix D Table 10. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden[a]	TB Risk Factors	Mean (Range) Age	% F	% Non-white	% BCG	Quality
		weeks); INH restart if missed doses >1 month									

[a] TB burden according to World Health Organization classification. Low <10 cases/100,000; intermediate 10–99 cases/100,000; high >100 cases/100,000.
[b] Countries classified as high TB according to TB incidence as suggested by the World Health Organization.
[c] Number of subjects who have been in close contact with an individual with active TB unspecified.
[d] Although TB burden in Canada is low, 54%–55% of the Canadian participants (a total of 462 participants) were born in countries with high TB incidence.
[e] Data extracted from supplemental data provided by personal communication source for eligible study subgroup (HIV-negative subjects with IGRA or TST confirmation).
[f] Inclusion criteria initially limited to ages 20–64 years, but a few persons are included outside these limits.
[g] Defined as well-delineated radiographic lesions of probable tuberculous origin, usually in the upper half of the lung, which had been stable during the year prior to entry. For participants, the lesions had been known to exist for a median of 8 years (range, 11 months to 58 years).
[h] Median induration of participants was 15 mm (range, 6–90 mm).
[i] Czechoslovakia (low), Finland (low), Germany (low), Hungary (intermediate), Poland (intermediate), Romania (intermediate), Yugoslavia (low-intermediate).

Abbreviations: BCG=bacille Calmette-Guérin; CXR=chest x-ray; F=female; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assays; INH=isoniazid; IUAT=International Union Against Tuberculosis; LTBI=latent tuberculosis infection; N=sample size; NR=not reported; RIF=rifampin; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test; Unk=unknown.

Appendix D Table 11. Characteristics of Included Randomized, Controlled Trials for Benefits (KQ 3), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Active TB Disease, N (%)	Transmission, N (%)	Quality of Life	Overall Mortality, N (%)	Disease-Specific Mortality, N (%)
Menzies, 2008[133] 847	RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months (420). INH 5 mg/kg, up to 300 mg/day x 9 months (427).	NR	NR	NR	0 (0) 1 (0.2)	0 (0) 0 (0)
Sterling, 2011[134] PREVENT TB 6,886	RPT 900 mg + INH 900 mg/week x 12 weeks (3,556). INH 300 mg/day x 36 weeks (3,330).	5 (0.15) 10 (0.32) Rate per 100 person years 0.05 0.12 Difference in cumulative TB rate -0.17 Upper bound of the 95% CI, (%) 0.07	NR	NR	30 (0.8) 34 (1.0)	NR
Thompson, 1982[135] IUAT 27,830	INH 300 mg x 12 weeks (6,956). INH 300 mg x 24 weeks (6,965). INH 300 mg x 52 weeks (6,919). Placebo (6,990).	76 (1.1) 34 (0.5) 24 (0.3) 97 (1.4) % reduction compared with placebo[a,b] 21 65 75 NA (reference) RR compared with 52 weeks of INH[c] 3.1 1.4 1.0 (reference) 4.0 Benefit-to-risk ratio by regimen (cumulative TB cases prevented/cumulative hepatitis cases incurred), 5 years: 1.2 2.6[d, e] 2.1 NA (reference)	NR	NR	All groups combined: 1124 (4.0) NR by group	Due to tuberculosis: 0 (0.00) 0 (0.00) 0 (0.00) 3 (0.042)

Appendix D Table 11. Characteristics of Included Randomized, Controlled Trials for Benefits (KQ 3), Main Analysis

[a] Percent reduction by size of lesion: for lesions <2 cm^2, 20, 66, 64, and NA (reference); for lesions >2 cm^2, 24, 67, 89, and NA (reference).
[b] When limited to "completer-compliers," the percent reductions were 31, 69, 93, and NA (reference), respectively.
[c] The differences between the 52-week and 24-week INH regimens and between the 12-week INH and placebo were not statistically significant (0.20 >P >0.10). All other interregimen differences were statistically significant.
[d] RR by size of lesion: for lesions <2 cm^2, 2.2, 1.0, 1.0 (reference), and 2.8; for lesions >2 cm^2, 6.8, 2.9, 1.0 (reference), and 8.9.
[e] When limited to "completer-compliers," the RRs were 9.4, 4.3, 1.0 (reference), and 13.6, respectively.

Abbreviations: INH=isoniazid; IUAT=International Union Against Tuberculosis; N=sample size; NA=not applicable; NR=not reported; RR=relative risk; TB=tuberculosis.

Appendix D Table 12. Characteristics of Included Randomized, Controlled Trials for Harms (KQ 5), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	DC Due to AEs, N (%)	Hepatotoxicity, N (%)	Mortality From Hepatotoxicity, N (%)	Gastrointestinal, N (%)	Other Specific AEs, N (%)[a]
Menzies, 2004[143] 116	RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months; up to 20 weeks, if needed, depending on missed doses (58) INH 5 mg/kg, up to 300 mg/day x 9 months; up to 43 weeks, if needed, depending on missed doses (58)	2 (3.4) 8 (13.8) RR: 0.25 (95% CI, 0.1 to 1.1)	0 (0) 3 (5.2) Drug-induced hepatitis after 74, 105, and 137 doses of INH	0 (0) 0 (0)	Severe nausea and vomiting: 4 (3.4)[b]	Other overall AEs 2 (3.4) 5 (8.6) Calculated RR: 0.40 (95% CI, 0.08 to 1.98) Persistent debilitating fatigue: 2 (1.7) Rash: 1 (0.8)[c]
Menzies, 2008[133] 847	RIF 10 mg/kg of body weight, up to 600 mg/day x 4 months (420) INH 5 mg/kg, up to 300 mg/day x 9 months (427)	Among protocol-adherent: 16 (3.8) 24 (5.6) Subtotal for any grade 3 or 4 AE[d-h] 7 (1.7) 17 (4.0) RD: -2.3% (95% CI, -5.0 to -0.1) Subtotal for any grade 1 or 2 AE:[i-m] 9 (2.1) 7 (1.6) RD: 1% (95% CI, 1.0 to 3.0)	Grade 3 or 4 hepatotoxicity[d] 3 (0.7) 16 (3.7) RD: -3.1% (95% CI, -5.0 to -1.0)	0 (0) 0 (0)	Minor AEs reported "similar" between groups GI intolerance (grade 1 or 2 AE):[l] 1 (0.2) 2 (0.5) Calculated RR: 0.51 (95% CI, 0.05 to 5.59)	Hematologic (grade 3 or 4 AE):[d] 2 (0.5) 1 (0.2) Calculated RR: 2.0. (95% CI, 0.19 to 22.34) Drug interaction (grade 3 or 4 AE):[h] 1 (0.2) 0 (0) Calculated RR: 3.05 (95% CI, 0.13 to 74.66) Rash (grade 3 or 4 AE)[e] 1 (0.2) 0 (0) Calculated RR: 3.05 (95% CI, 0.13 to 74.66) Rash (grade 1 or 2 AE)[j] 8 (1.9) 5 (1.2) Calculated RR: 1.63 (95% CI, 0.54 to 4.93)

Appendix D Table 12. Characteristics of Included Randomized, Controlled Trials for Harms (KQ 5), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	DC Due to AEs, N (%)	Hepatotoxicity, N (%)	Mortality From Hepatotoxicity, N (%)	Gastrointestinal, N (%)	Other Specific AEs, N (%)[a]
Sterling, 2011[134o] PREVENT TB 6,886	RPT 900 mg + INH 900 mg/week x 12 weeks (3,556) INH 300 mg/day x 36 weeks (3,330)	DC due to adverse drug reaction: 186 (5.2) 136 (4.1) Calculated RR: 1.28 (95% CI, 1.03 to 1.59)	Grade 3 toxicity:[p] 176 (4.9) 184 (5.5) Calculated RR: 0.90 (95% CI, 0.73 to 1.10) Grade 4 toxicity:[p] 34 (1.0) 35 (1.1) Calculated RR for Grade 3 or 4 toxicity: 0.90 (95% CI, 0.75 to 1.08)	Grade 5 (death): 30 (0.8) 34 (1.0) Calculated RR: 0.83 (95% CI, 0.51 to 1.35)	NR	Possible hypersensitivity: 146 (4.1) 17 (0.5) Calculated RR: 8.04 (95% CI, 4.88 to 13.26)
Thompson, 1982[135] IUAT 27,830	INH 300 mg x 12 weeks (6,956) NH 300 mg x 24 weeks (6,965) INH 300 mg x 52 weeks (6,919) Placebo (6,990)	Overall DC: INH (8.1) Placebo (5.8)[147] Due to AEs (GI distress, liver disease, or gallbladder disease): INH (1.8) Placebo (1.2)[147] DC due to liver disease: INH (0.4) Placebo (0.1)[147]	Hepatitis: INH 99[q] (0.5) Placebo 7 (0.1) Cumulative excess hepatitis rates per 1000 cases for INH: 12 weeks: 2.5 24 weeks: 3.6 52 weeks: 5.2 Calculated number of cases: 12 weeks: 24 24 weeks: 32 52 weeks: 43 Hepatitis cases prevented per 1000 persons by reducing duration of INH from 52 weeks to: 24 weeks: 1.6 12 weeks: 2.7	2 (0.03) 0 (0.00) 1 (0.01) 0 (0.00) 0.14 per 1,000 persons receiving INH 0 cases in placebo group. Calculated RR: 2.35 (95% CI, 0.12 to 45.46)	GI distress resulting in stopping: INH (1.2) Placebo (0.9)[147] Calculated RR: 1.33 (95% CI, 1.01 to 1.75)	Gallbladder disease resulting in stopping: INH (0.2) Placebo (0.2)

Appendix D Table 12. Characteristics of Included Randomized, Controlled Trials for Harms (KQ 5), Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	DC Due to AEs, N (%)	Hepatotoxicity, N (%)	Mortality From Hepatotoxicity, N (%)	Gastrointestinal, N (%)	Other Specific AEs, N (%)[a]
White, 2012[144] 364	RIF 600 mg/day x 4 months; up to 6 months, if needed, depending on missed doses for a total of 120 doses (180) INH 900 mg 2x/week x 9 months; up to 12 months, if needed, depending on missed doses for a total of 76 doses (184)	2 (1.1) 0 (0)	Grade 3 for LFT was AST or ALT >5.0–10.0 times ULN ≥3 elevated LFT: 8 (4.4) 21 (11.4)	0 (0) 0 (0)	GI 16 (9) 9 (10) Calculated RR: 1.82 (95% CI, 0.82 to 4.01)	Other AEs[c] Rash/pruritus 16 (9) 12 (6) Calculated RR: 1.36 (95% CI, 0.66 to 2.80) Central nervous system 6 (3) 20 (11) Calculated RR: 0.31 (95% CI, 0.13 to 0.75) Allergic reaction 1 (1) 0 (0) Calculated RR: 3.07 (95% CI, 0.13 to 74.78) Other[e] 13 (7) 14 (8) Calculated RR: 0.95 (95% CI, 0.46 to 1.96)

[a] No studies reported peripheral neuropathy or development of drug-resistant TB outcomes.
[b] Other adverse events not presented by drug regimen, but for entire population.
[c] Categories are not mutually exclusive; participants could experience symptoms in more than one body system category. Therefore, the number and percentage represent the number of participants and the percentage of the study group or total that had an adverse event in the category.
[d] Liver aminotransferase levels that increased to 5 to 10 or 3 to 10 times the upper limit of normal in the presence of compatible symptoms met criteria for grade 3 hepatotoxicity, whereas those that exceeded 10 times the upper limit of normal met criteria for grade 4 toxicity.
[e] Criteria for a grade 3 rash is a rash that affects 100% of body surface area or mucus membranes, conjunctivae are affected, vital signs are abnormal (fever or low blood pressure), or there is wheezing.
[f] Neutrophil counts <1.00 to 0.50 x 10^9 cells/L or platelet counts <50 to 25 x 10^9 cells/L met the criteria for grade 3 hematologic effects, whereas neutrophil counts that exceeded 0.50 x 109 cells/L or platelet counts greater than 25 x 109 cells/L met the criteria for grade 4.
[g] Protracted nausea and vomiting or severe abdominal pain that disrupts daily life (for example, cannot sleep), severe diarrhea (more than 5 bowel movements per day) met the criteria for a grade 3 gastrointestinal adverse event.
[h] Under drug interaction grade 3, drug interaction was noted and therapy was modified repeatedly but eventually successful; patient did not have any untoward clinical effect, and LTBI therapy was continued. Under grade 4, care providers unable to adjust therapy successfully to achieve therapeutic effects; LTBI therapy was discontinued.
[i] Liver aminotransferase levels that increased to 1 to 3 times the upper limit of normal in the presence of symptoms suggestive of hepatotoxicity (nausea, anorexia, vomiting, fatigue, abdominal pain) met criteria for grade 1, whereas levels 1 to 5 times the upper limit of normal with no symptoms met criteria for grade 2 toxicity.

[j] Criteria for a grade 1 rash involves itching only or limited to limbs, trunk, or face only; no abnormality of vital signs and no mucosal or conjunctival involvement. Grade 2 rash affects limbs and trunk or more than 50% of total body surface area or rash is confluent in areas.
[k] Neutrophil levels <1.50 to 1.00 x 10^9 cells/L or platelet counts <100 to 50 x 10^9 cells/L met the criteria for grades 1-2.
[l] Some stomach upset with nausea or loss of appetite, but no vomiting and no change in bowel habits met that criteria for a grade 1 gastrointestinal adverse event.
[m] Under drug interaction grade 1, a potential drug interaction was noted, but no change in therapy was required and neither short- nor long-term effect detected. Under grade 2, a potential drug interaction was noted, but after an initial change in therapy, no further problems and therapy did not have to be changed.
[n] Data extracted from supplemental data provided by personal communication source for eligible study subgroup (HIV-negative subjects with IGRA or TST confirmation).
[o] Other category includes symptoms such as appetite loss, muscle/body pain, fatigue, weight loss, malaise, cold symptoms, change of urine color, fever, and eye redness.
[p] Common toxicity criteria version 2.0. Bethesda, MD: Cancer Therapy Evaluation Program, 1999 (http://www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf).
[q] The total number of hepatotoxicity cases among isoniazid patients was calculated based on the cumulative excess hepatitis rates per 1000 cases for INH presented in the paper.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; DC=discontinuation; GI=gastrointestinal; INH=isoniazid; LFT=liver function test; N=sample size; NR=not reported; RD=risk difference; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis; ULN=upper limit of normal.

Appendix D Table 13. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses (KQs 3, 5)

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden[a]	TB Risk Factors	Mean (Range) Age	% F	% Non-white	% BCG	Quality
Bailey,1974[145] 178	INH 300 mg + 50 mg pyridoxine (vitamin B6)/day x 12 months (85) Control (93)	Rolling enrollment, followup ranged between 1 and 10 months	Adult tuberculin-reactive employees in a U.S. hospital (1900-bed general; 80 beds for TB patients) considered for anti-TB chemoprophylaxis with INH Normal levels (SGOT <40): 63 (74) 62 (67) Abnormal levels (SGOT ≥40): 22 (26) 31 (33)[b]	No, but positive TST (5 TU PPD); cut-off unspecified	U.S.: low	Health care workers: 178 (100%)	38.54 (13.78 SD) 40.56 (11.39 SD)	74.2	70.2	NR	Fair
Bush, 1965[43] All subjects: 2,238 ≥15 years: 1309 ≥20 years: 1140	INH 250 mg/day x 12 months (571) Placebo (569)	1 year after end of medication regimen	Subjects age ≥20 years who were HH contacts of active TB cases Total HHs: 328 322 HHs with ≥1 active TB cases: 220 189 Study population age ≥20 years: 569 571 Study population age ≥15 years: 646 663	No, but chest film and TST (5 TU PPD-S); 90% of adults with ≥5-mm TST	Japan: low	HH contacts (all ages) who lived with an adult index case for >9 months: (78.5) (78.9)	20-49 years: 818 ≥50 years: 322	59.4 (≥20 years)	NR; ~100%	NR	Fair

Appendix D Table 13. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses (KQs 3, 5)

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden[a]	TB Risk Factors	Mean (Range) Age	% F	% Non-white	% BCG	Quality
Byrd, 1977[146] 120	Round 1: INH 300 mg/day x 3 months (60) Placebo (60) Round 2: INH 300 mg/day x 3 months (60)[c]	3 months	Age ≥18 years with baseline SGOT <20 for Round 1; SGOT levels unspecified for Round 2 ATS criteria for undergoing chemoprophylaxis	Positive TST (between stabilized intermediate strength); cutoff unspecified; CXR	U.S.: low	NR	<30 years: 19 22 30-39 years: 23 25 >40 years 18 13	26.7	30	NR	Fair
Falk, 1978[41,148] 7,036	INH 300 mg/day x 2 years (2,166) INH 300 mg/day x 1 year, followed by placebo x 1 year (2,553) Placebo daily x 2 years (2,317)	7 years	Veterans with pulmonary TB classified as inactive[d, e]	NR; required to have inactive pulmonary TB	U.S.: low	NR	78% were 30-50 years; 16% were 51-70 years	2	24 23 21	NR	Fair
Ferebee, 1963[44] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in morbidity analyses[f,g]	INH 4-7 mg/kg/day (average of 5 mg/kg)[h] x 12 months (14,407 in randomized sample; 12,884 in morbidity analyses) Placebo x 12 months (13,517; 12,326)	10 years	Those residing in mental institutions	No (not required to have positive TST to be included; 57% had positive TST ≥5 mm)	U.S.[i]: low	Residing in mental institutions 100% Abnormal CXR 1216 (9.5%) 1071 (8.7%) Tuberculin positive 7242 (56%) 7253 (59%)	Males: 48 Females: 54 Listed overall range: 2-80+ years Proportion age <15 years: 63% 58%	51 54	13 11	NR	Fair
Veening, 1968[42] 261	INH 600 mg (8-10 mg/kg) x 4 months, then 400 mg (5-7 mg/kg) until 1 year (133)[j]. Placebo (128).	7 years	Military service members with Mantoux conversion after exposure to an active case	Yes	Netherlands; low	All were close contact of an active case	Mean NR; military recruits 18-20 years at baseline	0 (0) 0 (0)	NR	NR	Poor

[a] TB burden according to World Health Organization classification. Low <10 cases/100,000; intermediate 10–99 cases/100,000; high >100 cases/100,000.
[b] Chi-square=0.8479; P=0.30 (not significant, according to authors).
[c] Placebo subjects received treatment after initial 3-month trial.
[d] Determined by NTA diagnostic standards current at that time.

Appendix D Table 13. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses (KQs 3, 5)

[e] TB had been inactive for 5 years or more in 95% of participants.
[f] Morbidity analyses did not include patients who moved to a new ward and crossed over; only included people who took either INH or placebo.
[g] All data entered for Ferebee 1963 for subsequent rows of this table are based on the N included in morbidity analyses.
[h] Subjects age 15 years and older received 300 mg/day.
[i] Wisconsin, Georgia, Michigan, and Massachusetts.
[j] This is a higher dose than is currently recommended by the CDC.

Abbreviations: ATS=American Thoracic Society; BCG=bacille Calmette-Guérin; CXR=chest x-ray; F=female; HH=household; INH=isoniazid; LTBI=latent tuberculosis infection; N=sample size; NR=not reported; PPD=purified protein derivative; PPD-S=polysorbate 80 stabilized solution of tuberculin purified protein derivative; SD=standard deviation; SGOT=serum glutamic-oxalacetic transaminase; TB=tuberculosis; TST=tuberculin skin test; TU=tuberculin units.

Appendix D Table 14. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Benefits (KQ 3)

Author, Year Trial Name N	Drug, Dose X Duration (N)	Active TB Disease, N (%)	Transmission, N (%)	Quality of Life	Overall Mortality, N (%)	Disease-Specific Mortality, N (%)
Bush, 1965[43] All subjects: 2,238 ≥15 years: 1,309 ≥20 years: 1,140	INH 250 mg/day x 12 months (569). Placebo (571).	All subjects (adults and children): 8 (0.73)[a] 11 (0.96)[b] Subjects ≥15 years: 4 (0.60) 7 (1.08)	NR	NR	NR NR	NR NR
Falk, 1978[41,148] 7,036	INH 300 mg daily x 2 years (2166). INH 300 mg daily x 1 year, followed by placebo x 1 year (2,553). Placebo daily x 2 years (2,317).	17 (0.8) 20 (0.8) 26 (1.1) Among those with no prior treatment for TB (2,389 subjects): 8 5 15 Reactivators who had received previous treatment: 9 (0.6) 15 (0.9) 11 (0.7) Reactivators who had received previous adequate[c] treatment 5 13 5[d]	NR	NR	Total deaths: 357 Rate: 4/1,000 6.5/1,000 4.4/1,000 p=0.0001 for INH 1 year vs. placebo; NR for other comparisons	2 (0.03) deaths from TB (both received INH; 1 occurred at the 6th month of INH therapy and 1 in a patient who completed only 2 months of INH and died 11 months later)

Appendix D Table 14. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Benefits (KQ 3)

Author, Year Trial Name N	Drug, Dose X Duration (N)	Active TB Disease, N (%)	Transmission, N (%)	Quality of Life	Overall Mortality, N (%)	Disease-Specific Mortality, N (%)
Ferebee, 1963[44] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in morbidity analyses	INH 4-7 mg/kg/day (average of 5 mg/kg) x 12 months (14,407 in randomized sample; 12,884 analyzed). Placebo x 12 months (13,517; 12,326).	Cases diagnosed during first 15 months of the trial: Total 4 (0.03) 21 (0.17) Among those with abnormal CXR 3 (0.25) 14 (1.31) Among those who were tuberculin positive 0 (0.0) 7 (0.11) Tuberculin negative 0 (0.0) 0 (0.0) Unknown tuberculin status 1 (0.11) 0 (0.0) Cases developing after medication year Total 15 (0.12) 30 (0.24) Among those with abnormal CXR 5 (0.41) 9 (0.84) Among those who were tuberculin positive 5 (0.08) 17 (0.26) Cases appearing by May 1962 in subjects age ≥20 years in placebo group Males <150 lbs: 21 (1.14) Males ≥150 lbs: 3 (0.20) Females <130 lbs: 8 (0.46) Females ≥130 lbs: 2 (0.10) Cases based on TB infection status in placebo group: Initial tuberculin reactions <5 mm: 4 (0.10) Initial tuberculin ≥5 mm: 24 (0.37) Abnormal roentgenogram: 23 (2.15)	NR	NR	During treatment year, among the full randomized sample[e]: 752 (5.2) 611 (4.5) Among patients who took only 1 medication (excluding crossovers): 695 (5.4%) 547 (4.4%)	NR

Appendix D Table 14. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Benefits (KQ 3)

Author, Year Trial Name N	Drug, Dose X Duration (N)	Active TB Disease, N (%)	Transmission, N (%)	Quality of Life	Overall Mortality, N (%)	Disease-Specific Mortality, N (%)
Veening, 1968[42] 261	INH 600 mg (8-10 mg/kg) x 4 months, then 400 mg (5-7 mg/kg) until 1 year (133). Placebo (128).	1 year: 1 (0.8) 9 (7.0) 4 years: 1 (0.8) 12 (9.4) 7 years: 1 (0.8) 12 (9.4)	NR	NR	NR	NR

[a] No cases first 3 months after starting treatment; 1 case between months 6 and 11; 7 cases 11 months or more after starting treatment. Days index case in home by new cases: 1-60 days: 2; 61-180 days: 4; 181-270 days: 1; 270-300 days: 1.
[b] No cases first 3 months after starting treatment; 2 cases between months 6 and 11; 9 cases 11 months or more after starting treatment. Days index case in home by new cases: 1-60 days: 2; 61-180 days: 2; 181-270 days: 5; 270-300 days: 2.
[c] Adequate treatment was defined as at least 18 months of therapy with two drugs.
[d] Rate of reactivation was 7.3/1,000 for those with adequate prior chemotherapy and 12.7/1,000 for those with inadequate or no prior chemotherapy.
[e] Deaths in wards participating in the trial during the year prior to the trial: INH 801 (5.6), placebo 698 (5.2). Change in percent of deaths from year prior to the trial to the medication year: INH -0.4%; placebo -0.7%.

Abbreviations: CXR=chest x-ray; INH=isoniazid; N=sample size; NR=not reported; TB=tuberculosis.

Appendix D Table 15. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Harms (KQ 5)

Author, Year Trial Name N	Drug, Dose X Duration (N)	DC due to AEs, N (%)	Hepatotoxicity, N (%)	Mortality From Hepatotoxicity, N (%)	Gastrointestinal, N (%)	Other Specific AEs, N (%)[a]
Bailey,1974[145] 178	INH 300 mg + 50 mg pyridoxine (vitamin B_6)/day x 12 months (85). Control (93).	10 (11.8) NR	SGOT elevations ≥100 mU/mL[b]: 10 (11.8)[c] 0 (0.0)[d] Among INH with ≥100 mU/mL: Average age: 50.2 (SD 12.09) Among INH with <100 mU/mL: Average age: 36.99 (SD 13.3)	NR NR	NR	NR
Bush, 1965[43] All subjects: 2,238 ≥15 years: 1,309 ≥20 years: 1,140	INH 250 mg/day x 12 months (569). Placebo (571).	All ages: 8 (0.7) 12 (1.1)	NR NR	NR NR	GI (all ages): 8 (0.7) 3 (0.3) Calculated RR: 2.68 (95% CI, 0.71 to 10.04)	Other AEs (all ages) Rash: 0 (0.0) 3 (0.3) Calculated RR: 0.14 (95% CI, 0.01 to 2.77) Other, unspecified: 0 (0.0) 6 (0.5) Calculated RR: 0.08 (95% CI, 0.004 to 1.37)
Byrd, 1977[146] 120	Round 1: INH 300 mg/day x 3 months (60). Placebo (60). Round 2: INH 300 mg/day x 3 months (60).	Round 1 7 (11.7) 1 (1.7) Round 2 3 (5.0)	SGOT elevations ≥100 IU: Round 1: 3 (5.0) 0 (0.0) Round 2: 1 (1.7) SGOT elevations ≥30 IU, overall: Round 1: (18.3) (6.9) p<05 Round 2: (22.4) p<0.025 SGOT elevations ≥30 IU, by month: Round 1[e], month 1: (5.0) (3.3) p=NS Month 2: (14.0) (3.4) p≤0.05	Round 1: 0 (0) 0 (0) Round 2: NR	Round 1: Nausea: 2 (3.3) 1 (1.7) Calculated RR: 2.00 (95% CI, 0.19 to 21.47) Clay-colored stools: 6 (10.0) 3 (5.0) Calculated RR: 2.00 (95% CI, 0.52 to 7.63) Anorexia: 5 (8.3) 5 (8.3) Calculated RR: 1.00 (95% CI, 0.31 to 3.28) Round 2: NR for any gastrointestinal events	Other adverse effects; round 1: Muscle aching: 18 (30.0) 17 (28.3) Calculated RR: 1.06 (95% CI, 0.61 to 1.85) Joint aching: 14 (23.3) 11 (18.3) Calculated RR: 1.27 (95% CI, 0.63 to 2.57) Flulike symptoms: 8 (13.3) 10 (16.7) Calculated RR: 0.80 (95% CI, 0.34 to 1.89) Fever: 4 (6.7) 4 (6.7) Calculated RR: 1.00 (95% CI, 0.26 to 3.82)

Appendix D Table 15. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Harms (KQ 5)

Author, Year Trial Name N	Drug, Dose X Duration (N)	DC due to AEs, N (%)	Hepatotoxicity, N (%)	Mortality From Hepatotoxicity, N (%)	Gastrointestinal, N (%)	Other Specific AEs, N (%)[a]
			Month 3: (14.0) (1.7) p≤0.025 Round 2: NR by month			Chills: 9 (15.0) 5 (8.3) Calculated RR: 1.8 (95% CI, 0.64 to 5.06) Skin rash: 7 (11.7) 6 (10.0) Calculated RR: 1.17 (95% CI, 0.42 to 3.27) Dark urine: 6 (10.0) 0 (0.0) Calculated RR: 13.0 (95% CI, 0.75 to 225.75) Yellow cast to sclera: 1 (1.7) 1 (1.7) Calculated RR: 1.00 (95% CI, 0.06 to 15.62) Round 2: NR for any other specific AE
Falk, 1978[41,148] 7,036	INH 300 mg/day x 2 years (2,166). INH 300 mg/day x 1 year, followed by placebo x 1 year (2,553). Placebo daily x 2 years (2,317).	NR	1 (0.01) taking INH (NR which group); mild hepatitis that resolved after stopping INH 0 in placebo group	NR	NR (reported that nausea occurred equally among the 3 regimens)	Rash INH regimens: 44 (0.9) Placebo: 8 (0.3) Calculated RR: 2.7 (95% CI, 1.27 to 5.73)
Ferebee, 1963[44] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in these harms analyses	INH 4-7 mg/kg/day (average of 5 mg/kg) x 12 months (14,407 in randomized sample; 12,884 in harms analyses). Placebo x 12 months (13,517; 12,326).	Made “sick” from pills 141 (1.1) 58 (0.47)	NR	NR	NR	NR

Appendix D Table 15. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Harms (KQ 5)

[a] No studies reported peripheral neuropathy or development of drug-resistant TB outcomes.
[b] Statistical analysis yielded a chi-squared value of 9.15 and a p≤0.01.
[c] Comparison using Fisher's exact test for 2x2 contingency tables. Number of subjects not provided.
[d] Reported rate of elevated transaminases for the placebo group is based on the 90 individuals who had baseline SGOT <100, not on the full placebo group (N=93).
[e] Liver aminotransferase levels that increased to 5 to 10 or 3 to 10 times the upper limit of normal in the presence of compatible symptoms met criteria for grade 3 hepatotoxicity, whereas those that exceeded 10 times the upper limit of normal met criteria for grade 4 toxicity.

Abbreviations: AE=adverse event; DC=discontinuation; INH=isoniazid; IU=international units; N=sample size; NR=not reported; NS=not sufficient; SD=standard deviation; SGOT=serum glutamic-oxalacetic transaminase; TB=tuberculosis.

Appendix E Table 1. Quality Ratings for Studies of Accuracy and Reliability of Screening Tests for Tuberculosis (KQ 2)

Author, Year	Were selection criteria clearly described?	Was the spectrum of patients representative of the patients who will receive the test in primary care?	Were withdrawals from the study explained (post-enrollment)?	Was the screening test relevant and adequately described?	Was the reference test performed regardless of screening test result?	Were the reference standard and screening test interpreted independently?	Were methods for calculating accuracy clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how they were handled?	Quality Rating
Adetifa, 2007[58]	Partially	NA	Partially	Partially	Yes	NR	NA	Yes	Fair
Ak, 2009[70]	Yes	NA	NA	Yes	Yes	NR	Yes	Yes	Good
Bellete, 2002[116]	Partially	Yes	Yes	Yes	NA	NA	NA	NA	Fair
Berkel, 2005[54]	Yes	No	NA	No	No	NR	Partially	NA	Fair
Bienek, 2009[121]	Yes	Partially	Yes	Yes	NA	NR	Partially	Yes	Fair
Bocchino, 2010[74]	Partially	NA	NA	No	Yes	NR	NA	Yes	Fair
Boyd, 2011[79]	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Good
Bua, 2007[119]	No	NR	NA	Partially	NA	NR	NA	Yes	Fair
Chee, 2008[64]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Good
Cho, 2011[80]	Yes	NA	NA	Partially	Yes	Yes	Yes	Yes	Good
Cummings, 2009[132]	No	Partially	No	Yes	NA	NR	No	Yes	Poor
Dewan, 2007[59]	Yes	NA	Partially	Yes	Yes	NR	Yes	Yes	Fair
Dilektasli, 2010[75]	Yes	Partially	Yes	Partially	Yes	Partially	NA	Yes	Fair
Dorman, 2014[127]	Yes	No	Yes	Yes	NA	NR	Yes	Yes	Good
Erdem, 2014[99]	No	NA	NA	Yes	No	NR	No	NR	Fair
Eum, 2008[104]	Partially	NA	No	Yes	Yes	NR	Partially	No	Poor
Feng, 2013[91]	Partially	NA	Yes	Yes	Partially	NR	NA	Yes	Fair
Fietta, 2003[53]	Yes	Yes	NA	Yes	NR	NR	NA	NA	Fair
Franken, 2007[126]	No	No	No	Partially	NA	NR	Partially	No	Poor
Franken, 2009[128]	Yes	Partially	NA	Yes	NA	NR	NA	Yes	Fair
Goletti, 2006[56]	Yes	NA	NR	Partially	Yes	Yes	Yes	Partially	Fair
Harada, 2008[65]	Yes	NA	NA	Yes	Yes	NR	NA	Yes	Good
Higuchi, 2009[71]	Partially	NA	Yes	Yes	Yes	NR	NA	Yes	Fair
Janssens, 2007[60]	Yes	NA	NA	Yes	Yes	NR	Yes	No	Fair
Jeon, 2013[92]	Yes	NA	NA	Yes	Yes	NR	NA	No	Fair

Appendix E Table 1. Quality Ratings for Studies of Accuracy and Reliability of Screening Tests for Tuberculosis (KQ 2)

Author, Year	Were selection criteria clearly described?	Was the spectrum of patients representative of the patients who will receive the test in primary care?	Were withdrawals from the study explained (post-enrollment)?	Was the screening test relevant and adequately described?	Was the reference test performed regardless of screening test result?	Were the reference standard and screening test interpreted independently?	Were methods for calculating accuracy clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how they were handled?	Quality Rating
Kalantri, 2009[106]	No	NA	NA	Yes	Yes	NR	NA	No	Poor
Kamiya, 2013[112]	No	NA	Partially	Yes	Partially	NR	Yes	NA	Poor
Kang, 2007[102]	Partially	NA	NA	Partially	Partially	NR	No	No	Poor
Kang, 2005[55]	Partially	NA	NR	Yes	Partially	No	Partially	Yes	Fair
Katsenos, 2010[122]	Yes	Partially	NA	Yes	NA	Yes	Yes	Yes	Good
Kim, 2014[100]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Good
Kim, 2013[93]	Partially	Yes	NA	Yes	Partially	NR	Yes	Yes	Fair
Kim, 2011[81]	Yes	NA	NA	Yes	Yes	NR	NA	Partially	Good (QFT-GIT) Poor (TST)
Kobashi, 2008[66]	Partially	NA	Yes	Yes	Yes	NR	NA	Yes	Fair
Kobashi, 2009[107]	No	NA	NA	Partially	Yes	NR	NA	No	Poor
Kobashi, 2009[72]	Partially	NA	NA	Yes	Yes	NR	No	Partially	Fair
Kobashi, 2008[67]	Yes	NA	NA	Yes	Yes	NR	NA	Yes	Good
Kobashi, 2008[68]	Partially	NA	NA	Yes	Yes	NR	NA	Yes	Fair
Kobashi, 2012[88]	Yes	NA	Yes	Partially	Yes	NR	Yes	Yes	Fair
Lai, 2011[83]	Partially	NA	NA	Partially	Yes	NR	NA	Yes	Fair
Lai, 2011[82]	Partially	No	NA	Yes	Yes	NR	Yes	Yes	Fair
Lee, 2012[89]	Partially	NA	NA	Yes	Yes	Yes	Yes	Yes	Good
Lee, 2011[97]	Partially	No	NA	Partially	Yes	NR	NA	NR	Fair
Legesse, 2010[76]	Yes	No	NA	Yes	Yes	NR	Yes	Yes	Fair
Lempp, 2015[124]	No	NA	NA	Yes	No	NR	No	NR	Fair
Li, 2012[110]	Partially	NA	NA	Partially	No	Partially	Yes	Yes	Poor
Losi, 2007[61]	Partially	NA	NA	Partially	Yes	NR	Yes	Partially	Fair
Lui, 2011[84]	Yes	No	NA	Yes	Partially	Partially	Yes	Yes	Fair

Appendix E Table 1. Quality Ratings for Studies of Accuracy and Reliability of Screening Tests for Tuberculosis (KQ 2)

Author, Year	Were selection criteria clearly described?	Was the spectrum of patients representative of the patients who will receive the test in primary care?	Were withdrawals from the study explained (post-enrollment)?	Was the screening test relevant and adequately described?	Was the reference test performed regardless of screening test result?	Were the reference standard and screening test interpreted independently?	Were methods for calculating accuracy clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how they were handled?	Quality Rating
Mancuso, 2012[123]	Partially	No	Yes	Yes	NA	Yes	Partially	No	Fair
Mazurek, 2007[62]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Good
Mazurek, 2007[120]	Yes	Yes	Yes	Yes	NA	NR	No	No	Fair
Mazurek, 2001[115]	Yes	Yes	NA	Yes	NA	NA	NA	NA	Good
Memish, 2000[101]	No	NA	NA	No	NR	NR	NA	NA	Poor
Metcalfe, 2010[77]	Yes	NA	Yes	Yes	Partially	NR	Partially	Yes	Fair
Min, 2013[94]	No	NR	NA	Yes	Yes	NR	Yes	Partially	Poor (Sp) Fair (Sn)
O'Shea, 2014[131]	Yes	No	NA	Yes	Yes	NR	Yes	Partially	Fair
Ozekinci, 2007[103]	Partially	Yes	NA	No	Yes	NR	No	Yes	Poor
Pai, 2007[63]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Good
Painter, 2013[51]	Yes	NA	Partially	Yes	Yes	Yes	Partially	No	Fair
Palazzo, 2008[105]	Partially	Partially	No	No	Yes	NR	Partially	No	Poor
Park, 2009[73]	Partially	Partially	Yes	Partially	Partially	NR	Partially	Yes	Fair
Qian, 2013[95]	Yes	NA	NA	Yes	Yes	NR	NA	No	Fair
Ra, 2011[85]	Partially	No	NA	Partially	Yes	NR	No	Yes	Fair (QFT-G) Poor (TST)
Ruhwald, 2011[86]	Yes	Partially	NA	Yes	Yes	NR	NA	Yes	Good
Seibert, 1991[52]	Partially	NA	Partially	Yes	Yes	NR	NA	NA	Fair
Shalabi, 2009[108]	Partially	NR	NA	No	Yes	NR	NA	NA	Poor
Shrestha, 2011[109]	No	NA	NA	Partially	Yes	NR	NA	Yes	Poor
Soysal, 2008[69]	Yes	Partially	No	Yes	Yes	NR	Partially	Partially	Fair
Taggart, 2006[118]	Yes	Partially	NA	Yes	NA	NR	Partially	No	Fair

Appendix E Table 1. Quality Ratings for Studies of Accuracy and Reliability of Screening Tests for Tuberculosis (KQ 2)

Author, Year	Were selection criteria clearly described?	Was the spectrum of patients representative of the patients who will receive the test in primary care?	Were withdrawals from the study explained (post-enrollment)?	Was the screening test relevant and adequately described?	Was the reference test performed regardless of screening test result?	Were the reference standard and screening test interpreted independently?	Were methods for calculating accuracy clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how they were handled?	Quality Rating
Taggart, 2004[117]	Partially	Yes	Yes	Yes	NA	NA	NR	NA	Fair
Taki-Eddin, 2012[90]	Partially	NA	NA	Yes	Yes	NR	NA	NR	Fair
Tan, 2010[78]	Partially	NA	NA	Yes	Yes	NR	NA	Yes	Fair
Tsiouris, 2006[57]	Yes	NA	NR	Yes	Yes	Yes	Yes	Yes	Good
Turtle, 2012[111]	No	NA	Partially	Partially	NR	NR	No	No	Poor
Villarino, 2000[114]	Partially	Partially	Yes	Partially	NA	Yes	NA	Yes	Fair
Villarino, 1999[113]	Partially	Partially	Yes	Yes	NA	Partially	NA	Partially	Fair
Walsh, 2011[87]	Yes	NA	NA	Partially	NR	NR	No	Yes	Fair
Wang, 2013[96]	Yes	NA	NA	Yes	Yes	NR	Yes	No	Fair
Whitworth, 2014[130]	Partially	Yes	NA	Yes	NA	NR	Yes	Yes	Fair
Whitworth, 2012[129]	Partially	NA	NA	Yes	Yes	NR	Yes	Yes	Good
Wlodarczyk, 2014[98]	Partially	Partially	Yes	Yes	NA	NR	Yes	Yes	Good

Good: Relevant and adequately described study populations for the outcome of interest (i.e., sensitivity, specificity), screening test well described in terms of test procedures followed and threshold used for a "positive" or "negative" test, credible reference standard used for outcome of interest (i.e., sensitivity or specificity), generally interprets reference standard independently of screening test, outcomes clearly reported and valid, handles indeterminate results in a reasonable manner.

Fair: Mostly includes a relevant and adequately described study population for the outcome of interest (i.e., sensitivity, specificity), screening test described although may include some ambiguity about test procedures followed or threshold for a "positive" or "negative" test, credible reference standard mostly used for outcome of interest (i.e., sensitivity or specificity), interpretation of reference standard may or may not be independent of screening test, outcomes mostly clearly reported although may have some ambiguity regarding how indeterminate results were handled.

Poor: Has fatal flaw such as study population not appropriate for outcome of interest (i.e., sensitivity, specificity), screening test improperly administered or not at all described, use of noncredible reference standard, reference and screening test not independently assessed, outcomes not clearly or accurately reported with no information about how indeterminate tests were handled.

Abbreviations: NA=not applicable; NR=not reported; QFT-GIT=QuantiFERON-TB Gold In-Tube (3rd generation test); Sn=sensitivity; Sp=specificity; TST=tuberculin skin test.

Appendix E Table 2. Quality Ratings for Randomized, Controlled Trials (KQs 3, 5): Main Analysis, Part 1

Author, Year Trial name N	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was adherence to the intervention adequate?	What was the overall attrition?	What was the differential attrition?	Did the study have differential or overall high attrition raising concern for bias?	Did the study have crossovers or contamination raising concern for bias?
Menzies, 2004[143] 116	Yes	Partially	Yes	Yes. RIF: 53 (91) took 80% of doses, 50 (86) took >90% of doses within 20 weeks INH: 44 (76) took 80% doses; 36 (62) took 90% of doses within 43 weeks 80% of doses: RR, 1.2 (95% CI, 1.02 to 1.4) 90% of doses: RR, 1.4 (95% CI, 1.1 to 1.7)	Did not complete: 19 (16.4) Dropout/default: 9 (7.8) RR: 0.5 (95% CI, 0.1 to 1.9)	Total did not complete: RIF: 5 (9) INH: 14 (24) Dropout/default: RIF: 3 (4) INH: 6 (10) RR: 0.5 (95% CI, 0.1 to 1.9)	Partially	No
Menzies, 2008[133] 847	Yes	Yes	Yes	Yes	Not included in primary analyses for serious AEs: 8 (0.9%) Stopped therapy early and were followed; nonprotocol-adherent: 205 (24%) Stopped therapy early and were followed; protocol-adherent: 45 (5.3%) Did not complete therapy: 264 (31%)	Not included in primary analyses for serious AEs: RIF 2 (0.5%) INH 6 (1.4%) Stopped therapy early and were followed; nonprotocol-adherent: RIF 72 (17%) INH 133 (31%) Stopped therapy early and were followed; protocol-adherent: RIF 17 (4.0%) INH 28 (6.6%) Did not complete therapy: RIF 92 (22%) INH 172 (40%)	No	No

Appendix E Table 2. Quality Ratings for Randomized, Controlled Trials (KQs 3, 5): Main Analysis, Part 1

Author, Year Trial name N	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was adherence to the intervention adequate?	What was the overall attrition?	What was the differential attrition?	Did the study have differential or overall high attrition raising concern for bias?	Did the study have crossovers or contamination raising concern for bias?
Sterling, 2011[134a] PREVENT TB 6,886	Partially	NR	Yes	Yes	Treatment completion:[a] 2895 (80.8%) 2264 (68.2%)	Differential treatment completion:[a] 12.6%	Partially	No
Thompson, 1982[135] IUAT 27,830	Yes	Yes	Unclear	Yes	5-year followup not complete for 781 (2.8%)	<5%	No	No
White, 2012[144] 364	Yes	Partially	Yes	No, nearly 1/2 of participants started on either INH or RIF were lost to followup by transfer to another facility or deportation Adherence higher for those who remained in jail: RIF: (79) INH: (83)	Did not complete: 257 (70.6)	Did not complete: RIF:120 (66.7) INH: 137 (74.5) Lost/withdrawn: RIF: 33 (18.3) INH: 44 (23.9) Deported/ transferred: RIF: 85 (47.2) INH: 93 (50.5) Withdrawn by physician: RIF: 2 (1.1) INH: 0 (0)	Yes	No

[a] Data extracted from supplemental data provided by personal communication source for eligible study subgroup (HIV-negative subjects with IGRA or TST confirmation).

Abbreviations: AE=adverse event; CI=confidence interval; INH=isoniazid; IUAT=International Union Against Tuberculosis; N=sample size; RIF=rifampin; RR=relative risk.

Appendix E Table 3. Quality Ratings for Randomized, Controlled Trials (KQs 3, 5): Main Analysis, Part 2

Author, Year Trial name N	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use an ITT analysis?	Did the study use acceptable statistical methods?	Quality Rating	Comments (Explain Poor Ratings)
Menzies, 2004[143] 116	Yes	No	No	No	No	Yes	Yes	Yes	Fair	Open label; authors state unblinded study justified because the primary study outcome, treatment completion, was likely strongly influenced by duration of therapy. Primary outcome was % prescribed doses taken as measured by electronic device in the pill container cap; patient compliance may be overestimated. Duration of treatment may have influenced judgment of severity of more subjective AEs (e.g., fatigue, nausea).
Menzies, 2008[133] 847	Yes	No	No	Yes, blinded review panel	Yes	Yes	Yes	Yes	Good	Open label, but used fairly rigorous methods with masked review panel to ascertain AEs.
Sterling, 2011[134] PREVENT TB 6,886	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Fair	Masking unclear and higher overall attrition.
Thompson, 1982[135] IUAT 27,830	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good (for KQ3) Fair (for KQ5)	
White, 2012[144] 364	Yes	No	No	No	No	Yes	Yes	Yes	Fair	Open label; nearly 1/2 of participants started on either INH or RIF were lost to followup by transfer to another facility or deportation. However, those who remained in jail had higher adherence.

Abbreviations: AE=adverse event; INH=isoniazid; ITT=intention to treat; IUAT=International Union Against Tuberculosis; RIF=rifampin.

Appendix E Table 4. Additional Quality Ratings for Randomized, Controlled Trials for Harms (KQ 5): Main Analysis

Author, Year Trial Name N	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Harms Quality Rating	Comments (Explain Poor Quality Ratings)
Menzies, 2004[143] 116	Yes	Yes	Partially	No	Fair	Followup likely insufficient; some AEs subject to judgment of severity (e.g., fatigue, nausea)
Menzies, 2008[133] 847	Yes	Yes	Yes	Yes	Good	
Sterling, 2011[134] PREVENT TB 6,886	Yes	Yes	Yes	Yes	Fair	
Thompson, 1982[135] IUAT 27,830	Partially; INH-induced hepatotoxicity was prespecified, NR how it was defined; unclear for other harms	Partially; specific criteria for ascertaining/ confirming hepatotoxicity NR	They were equal. Unclear how valid and reliable (dispensary staff were told to be particularly alert for symptoms of INH-induced hepatitis; participants were advised to call the dispensary if they had any unexpected reactions)	Yes	Fair	
White, 2012[144] 364	Yes	Yes	Yes	No	Fair	Nearly 1/2 of participants started were lost to followup by transfer to another facility or deportation, thus unable to adequately track harms

Abbreviations: INH=isoniazid; IUAT=International Union Against Tuberculosis; N=sample size; NR=not reported.

Appendix E Table 5. Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis (KQs 3, 5), Part 1

Author, Year Trial name N	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was adherence to the intervention adequate?	What was the overall attrition?	What was the differential attrition?	Did the study have differential or overall high attrition raising concern for bias?	Did the study have crossovers or contamination raising concern for bias?
Bailey,1974[145] 178	Yes; random assignment, although no details on methods	No; control group not given placebo	Partially, although baseline characteristics sparse. Control group had higher proportion of subjects with elevated SGOT levels at baseline.	Adherence levels NR	NR	NR	Attrition rates not report, thus unable to assess bias	Partially
Bush, 1965[43] All subjects: 2,238 ≥15 years 1309 ≥20 years 1140	Partially, randomized by HH instead of by individual	Partially, since randomized by HH, plausible families realized whether they were under treatment regimen	Partially, subjects randomized by HH. Baseline characteristics details sparse	Yes. Completed 9 months of drug regiment; all subjects (all ages): 780 (68.3) 748 (68.3) Completed 12 months of drug regiment; all subjects: 557 (48.8) 609 (55.6)	Total discontinued treatment; all subjects 441	Total discontinued treatment; all subjects 215 (18.8) 226 (20.6) Reasons for discontinuing treatment; all subjects: Moved or left household 46 (4.0) 48 (4.4) Not interested: 48 (4.2) 62 (5.6) Suspected TB: 2 (0.2) 2 (0.2) Non-TB illness: 13 (1.1) 14 (1.3) Busy: 18 (1.6) 17 (1.5) Forgot: 32 (2.6) 31 (2.8) Other reason: 42 (3.7) 37 (3.4) No reason given: 6 (0.5) 3 (0.3)	Partially	Yes; randomization at HH level

Appendix E Table 5. Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis (KQs 3, 5), Part 1

Author, Year Trial name N	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was adherence to the intervention adequate?	What was the overall attrition?	What was the differential attrition?	Did the study have differential or overall high attrition raising concern for bias?	Did the study have crossovers or contamination raising concern for bias?
Byrd, 1977[146] 120	Yes	Round 1: Yes, double-blinded; only chief hospital pharmacist knew content of pills. Same appearance/ imprint for both intervention and control Round 2: No, no concealment	Round 1: Yes Round 2: No, baseline SGOT levels not given for baseline; patients had progressed 3 months in to disease	Round 1 & 2: No, index of treatment compliance based on positive INH in monthly urine specimens. Patients could feasibly register positive if medication taken shortly before followup visit and not throughout month, thus not a true indicator of 30-day compliance	NR	NR	Attrition rates NR, thus unable to assess bias	Round 1: No Round 2: Partially, given prior 3 months as placebo arm
Falk, 1978[41,148] 7,036	Yes	Yes	Unclear. Article reports the groups were “balanced,” but no further details given by group other than race information.	Yes (78% completed >12 months of pill taking; 75% completed ≥19 months of pill taking; 73% completed the full 24 months)	19% (81% were observed for ≥5 years) 19%=1337 participants	NR. Stated distribution of factors related to stopping pill-taking were “similar” among the groups, but no information about differences/similarities in completion of followup or for missing data	Yes	Unclear

Appendix E Table 5. Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis (KQs 3, 5), Part 1

Author, Year Trial name N	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was adherence to the intervention adequate?	What was the overall attrition?	What was the differential attrition?	Did the study have differential or overall high attrition raising concern for bias?	Did the study have crossovers or contamination raising concern for bias?
Ferebee, 1963[44] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in morbidity analyses	Yes	Yes	Yes	Reported completion of >39 weeks (from records of ward attendants): INH 70.9% Placebo 76.4% Percentage of ward attendant records accepted as "probably correct": INH 66% Placebo 69%	Subjects crossing over were dropped from most analyses (except for some of the mortality analyses): n=2714 (9.7%) For the 12-month exam, health status was unknown for <0.05% of participants in the morbidity analyses	Subjects crossing over who were dropped from most analyses: 1.8% For the 12-month exam, unknown health status: <0.05%	No	Yes; 1191 (8.8%) patients from wards randomized to placebo spent part of the year on INH (e.g., transferred to a ward where INH was being given) and 1523 (10.6%) randomized to INH also received some placebo
Veening, 1968[42] 261	Unclear. No details given other than that they were divided "at random"	NR	NR, no data provided to allow comparability of groups at baseline	NR	Missing data for 51 (19.5%) at 7 years; unclear how much missing data for earlier time points, but implied 0% at 1 year; and 43 (16.5%) left military service in the first half	NR	Yes, moderate concern for risk of attrition bias for overall attrition for the later time points (4 years and 7 years); unclear for differential attrition	No

Appendix E Table 5. Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis (KQs 3, 5), Part 1

Author, Year Trial name N	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	Was adherence to the intervention adequate?	What was the overall attrition?	What was the differential attrition?	Did the study have differential or overall high attrition raising concern for bias?	Did the study have crossovers or contamination raising concern for bias?
					of year 2, but unclear how many of those were lost to followup			

Abbreviations: HH=household; INH=isoniazid; N=sample size; NR=not reported; SGOT=serum glutamic-oxalacetic transaminase; TB=tuberculosis.

Appendix E Table 6. Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis (KQs 3, 5), Part 2

Author, Year Trial name N	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use an ITT analysis?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Bailey,1974[145] 178	Yes	No	No	No	No	Partially	No	No	Fair	Adherence to treatment and data points for followup unclear
Bush, 1965[43] All subjects: 2,238 ≥15 years 1309 ≥20 years 1140	No, data by age group varied	Yes	Yes	Yes	Yes	Yes	No	No	Fair	Randomly assigned double-blind study; subjects randomized by HH groups; low retention; data presented inconsistently
Byrd, 1977[146] 120	Round 1: Yes Round 2: No, unclear baseline SGOT levels	Round 1: Yes Round 2: No	Round 1: Yes Round 2: No	Round 1: Yes Round 2: No	Round 1: No Round 2: No	Round 1: Partially Round 2: Partially	Round 1: Partially Round 2: Partially	Round 1: Partially Round 2: Partially	Fair	Round 1 randomly assigned double-blind study; Round 2 prospective cohort study, Study data difficult to discern in some outcomes (whether Round 1 and 2 treatment results were or were not combined; percentages given without n); adherence to treatment questionable in both rounds
Falk, 1978[41,148] 7,036	Yes, they were equal; used a masked referee to review all reports of TB reactivation; somewhat unclear what the exact criteria were (reports only that it was "by x-ray, positive bacteriology, or both")	Yes	Yes	Yes	Yes	No (appears nothing done to consider missing data; NR how much missing data there really was because no information about attrition by study group or about how much followup time subjects contributed)	Yes	Unclear	Fair	Good methods of randomization, allocation concealment, and masking; inadequately described statistical analyses; inadequate description of baseline characteristics to allow for assessment of comparability of groups at baseline (but methods of randomization and allocation concealment were good and the trial is very large). Overall attrition almost 20%; information NR about differential attrition; moderate concern for risk of bias due to attrition

Appendix E Table 6. Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis (KQs 3, 5), Part 2

Author, Year Trial name N	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Did the study use an ITT analysis?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Ferebee, 1963[44] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in morbidity analyses	Yes	Yes	Yes	Yes	Yes	NR (but seems that nothing was done to handle missing data)	No, dropped crossovers from analyses (more like a per protocol analysis)	Did not report data allowing a true ITT analysis, given how crossovers were handled	Fair	
Veening, 1968[42] 261	Unclear, methods of determining cases of active TB not clearly specified (they did x-rays every 2 months during the earlier part of the study; after 7 years they did x-rays, tracheal lavage, and urine, but article does not report criteria for case definition)	Yes	Yes	NR (study was reported as double-blind, but no information about outcome assessor masking)	Yes	NR, appears nothing done to handle missing data	Yes	Yes	Poor	Very limited reporting to allow risk of bias assessment in this 2-page publication; concern for risk of selection bias, attrition bias, confounding, and measurement bias given the very limited information provided; unclear if groups similar at baseline; unclear methods for randomization, allocation concealment, masking, and ascertainment of outcomes

Abbreviations: HH=household; ITT=intention to treat; N=sample size; NR=not reported; SGOT=serum glutamic-oxalacetic transaminase; TB=tuberculosis.

Appendix E Table 7. Additional Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis for Harms

Author, Year Trial name N	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Harms Quality Rating	Comments
Bailey,1974[145] 178	Yes	Yes	Yes	No	Fair	Adherence to treatment and data points for followup unclear
Bush, 1965[43] All subjects: 2,238 ≥15 years: 1309 ≥20 years: 1140	Yes	No	No	Yes	Poor	Low retention; thus, full extent of harms unavailable in data
Byrd, 1977[146] 120	Round 1: Yes Round 2: Partially	Round 1: Partially, although unclear if INH patient data presenting SGOT values by symptoms were limited to Round 1 INH patients Round 2: No; unclear if INH patient data presenting SGOT values by symptoms included Round 2 INH patients; data limited to those who had high SGOT levels and/or DC treatment	Round 1: Yes Round 2: Partially	Round 1: Yes Round 2: Partially	Fair	Patients only followed for 3 months of 3-month treatment; limited data presented from Round 2
Falk, 1978[41,148] 7,036	No	No	No	Yes	Poor	No consistent method for obtaining information on harms No followup labs or other formal process to adequately assess for elevated LFTs, hepatotoxicity, or other AEs They surveyed the investigators to determine any known cause of toxicity (unclear, but seems to have been a post-hoc survey; and no further information about what the survey contained or how the investigators collected information to respond to the survey)

Appendix E Table 7. Additional Quality Ratings for Randomized, Controlled Trials Used Only in Sensitivity Analysis for Harms

Author, Year Trial name N	Were harms prespecified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Harms Quality Rating	Comments
Ferebee, 1963[44] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in morbidity analyses	No	No	NR	Yes	Poor	Only harm reported is number stopping pills because they were made “sick” from the pills

Abbreviations: AE=adverse event; DC=discontinuation; INH=isoniazid; LFT=liver function test; SGOT=serum glutamic-oxalacetic transaminase.

Appendix E Table 8. Quality Ratings for Observational Studies Used Only in Sensitivity Analysis for Harms (KQ 5), Part 1

Author, Year Study Design	Were eligibility criteria clearly described?	Were subjects representative of the overall source population?	Did the study apply inclusion/ exclusion criteria uniformly to all comparison groups of the study?	Did the study avoid inappropriate exclusions?	Is the selection of the comparison group appropriate, after taking into account feasibility and ethical considerations?	Did the study guard against risk of survivor bias?	Were groups similar at baseline?	Were outcome assessors masked to the exposure status of participants?	What was the overall attrition?	What was the differential attrition?	Did the study have high attrition raising concern for bias?
Polesky 1996[156] Retrospective cohort 87	Yes	NR (no data provided on the source population)	Yes	Yes	Yes	Yes	Yes, as reported, but baseline data not available for all subjects (e.g., limited data available on HIV status, IV drug use)	No	14%	27 patients reported lost to followup immediately after skin test conversions in the no-therapy group (38%); 0 (0) in other groups	Not overall, but high differential attrition when compared with the no-therapy group

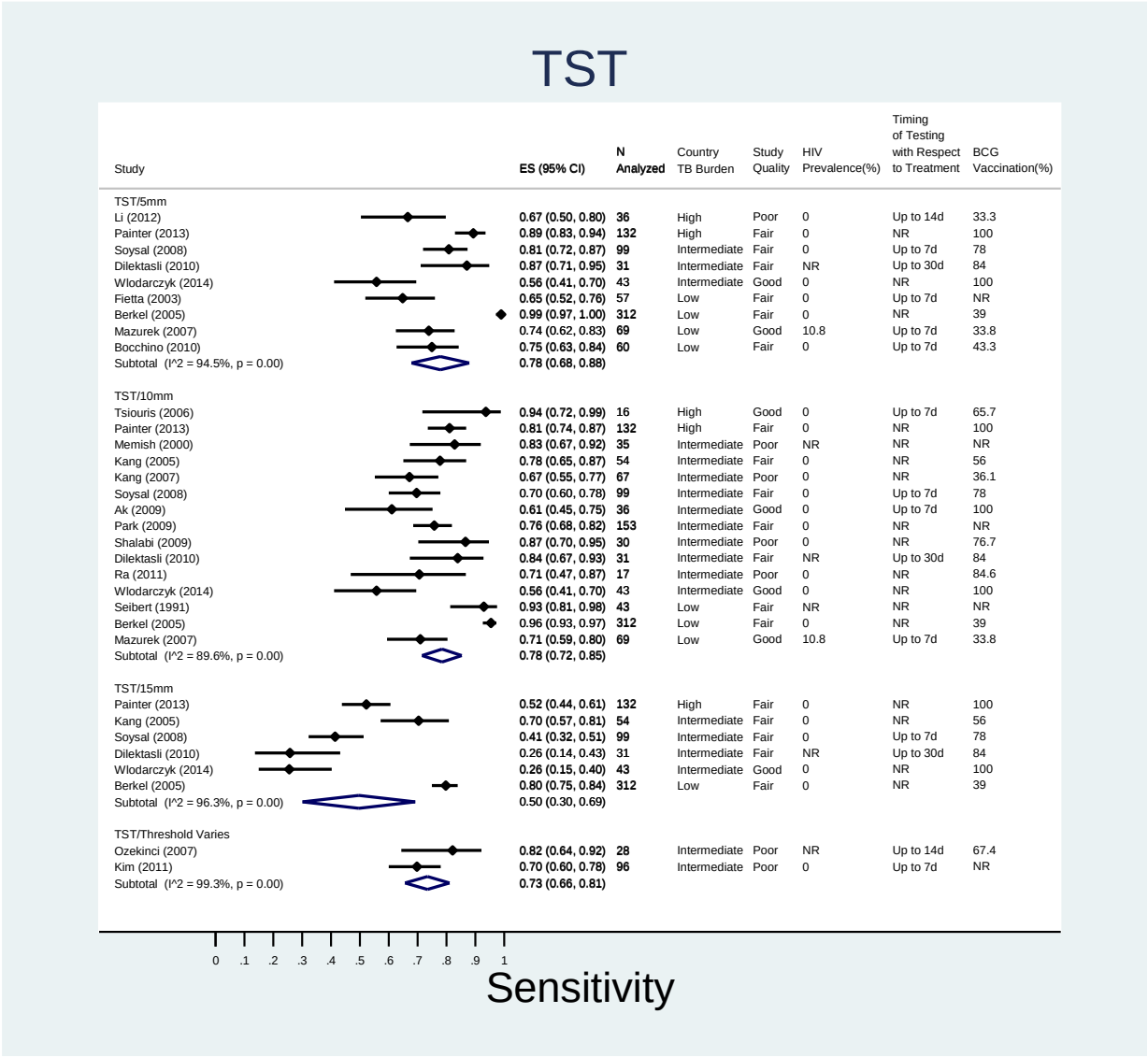
Abbreviations: HIV=human immunodeficiency virus; IV=intravenous; NR=not reported.

Appendix E Table 9. Quality Ratings for Observational Studies Used Only in Sensitivity Analysis for Harms (KQ 5), Part 2

Author, Year Study Name	Were harms pre-specified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques (outcome measures) for harms equal, valid, and reliable?	Was the duration of followup adequate to assess the outcome?	Does the analysis control for baseline differences between groups?	Does the analysis control for potential confounders?	Was an appropriate method used to handle missing data?	Did the study use appropriate statistical methods?	Quality Rating	Comments
Polesky, 1996[156] Retrospective cohort 87	No	No	NR, Unclear	Yes	No; and they had limited information available to determine similarity of groups at baseline	No	NR; for harms information, it is unclear how much missing data there were	Yes	Poor	Retrospective study designed aiming to assess benefits; methods for ascertaining harms not adequately described; high risk of selection bias and confounding Frequency of harms in no-treatment group was not reported for comparison; some differences in followup for those in the TB clinic

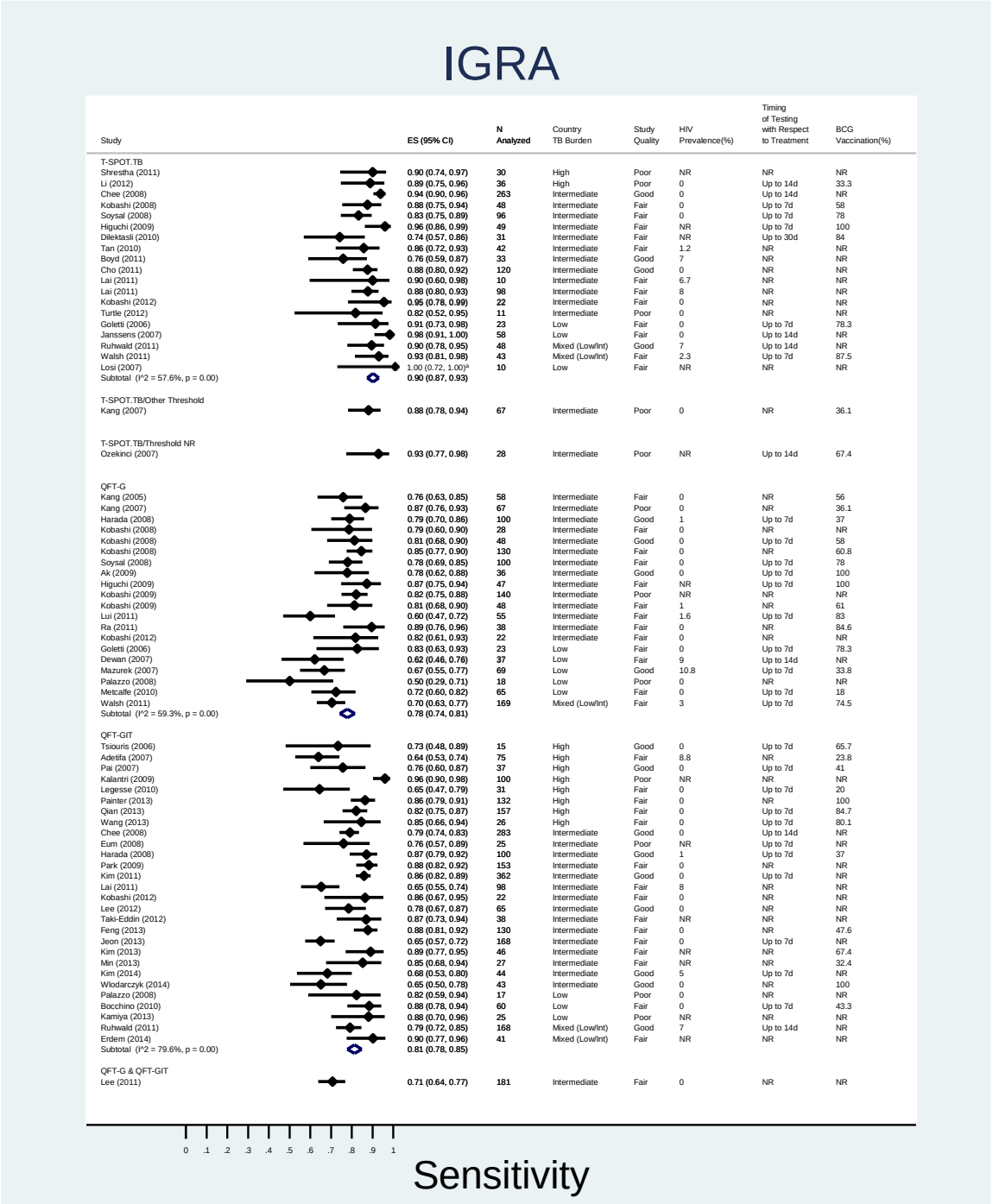
Abbreviations: NR=not reported; TB=tuberculosis.

Appendix F Figure 1. Sensitivity for Various Thresholds of TST for Tuberculosis Infection, Including Poor-Quality Studies



Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

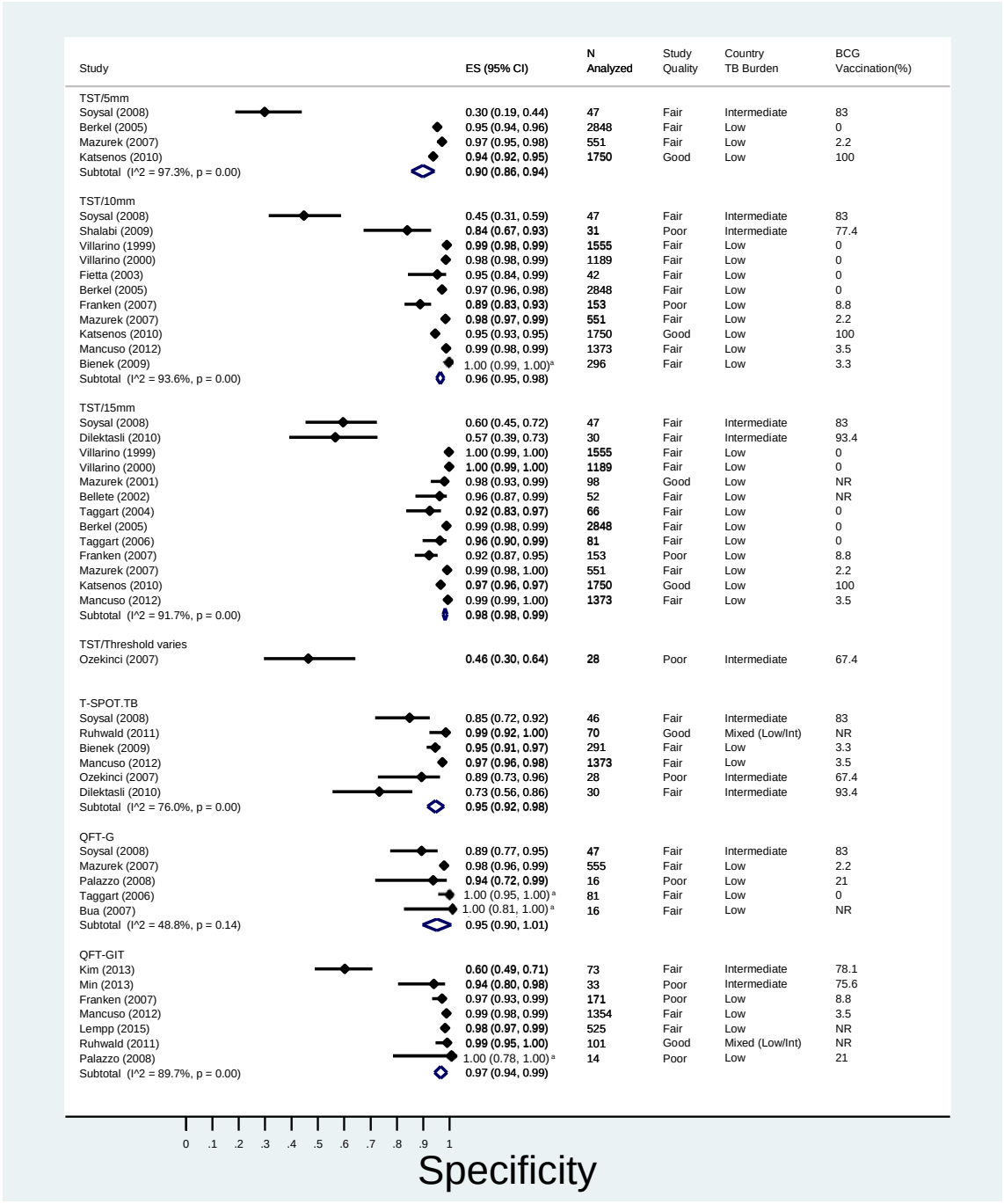
Appendix F Figure 2. Sensitivity for Various Thresholds of IGRA Tests for Tuberculosis Infection, Including Poor-Quality Studies



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

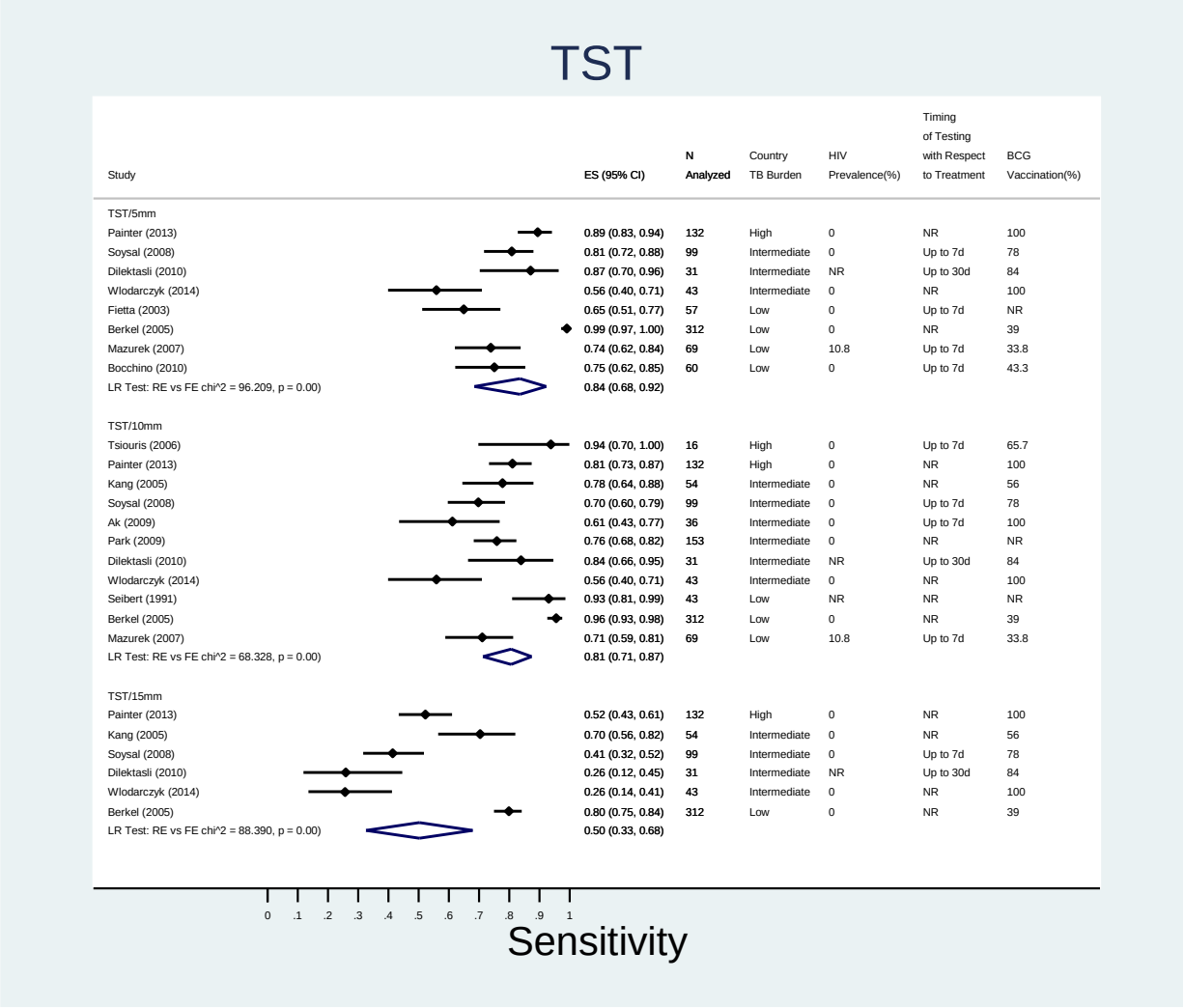
Appendix F Figure 3. Specificity for Various Thresholds of TST and IGRA Tests for Tuberculosis Infection, Including Poor-Quality Studies



[a] Excluded from pooled estimate due to point estimate of 1.0.

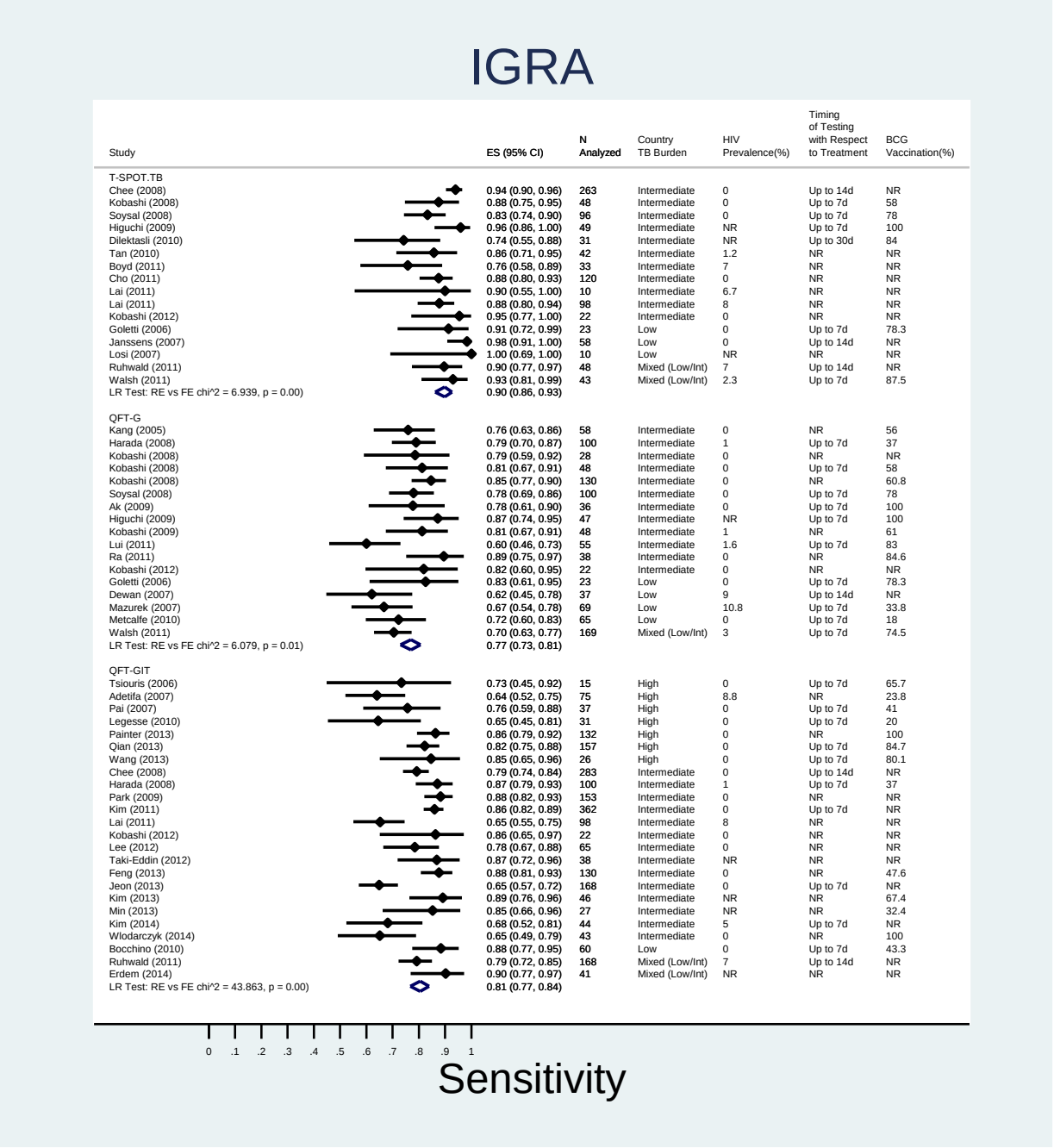
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 4. Sensitivity for Various Thresholds of TST for Tuberculosis Infection Using Maximum Likelihood Random-Effects Model



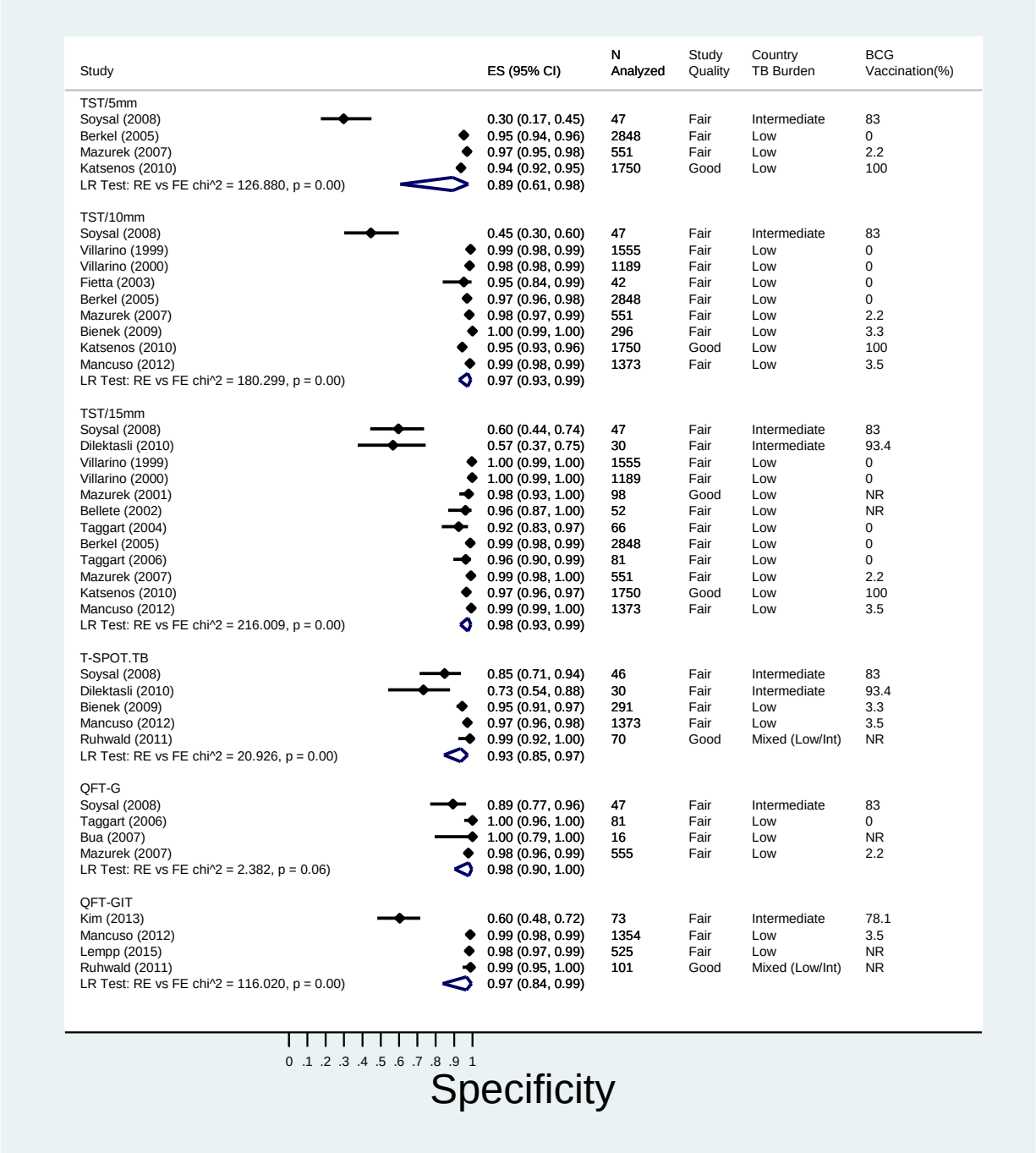
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 5. Sensitivity for Various Thresholds of IGRA Tests for Tuberculosis Infection Using Maximum Likelihood Random-Effects Model



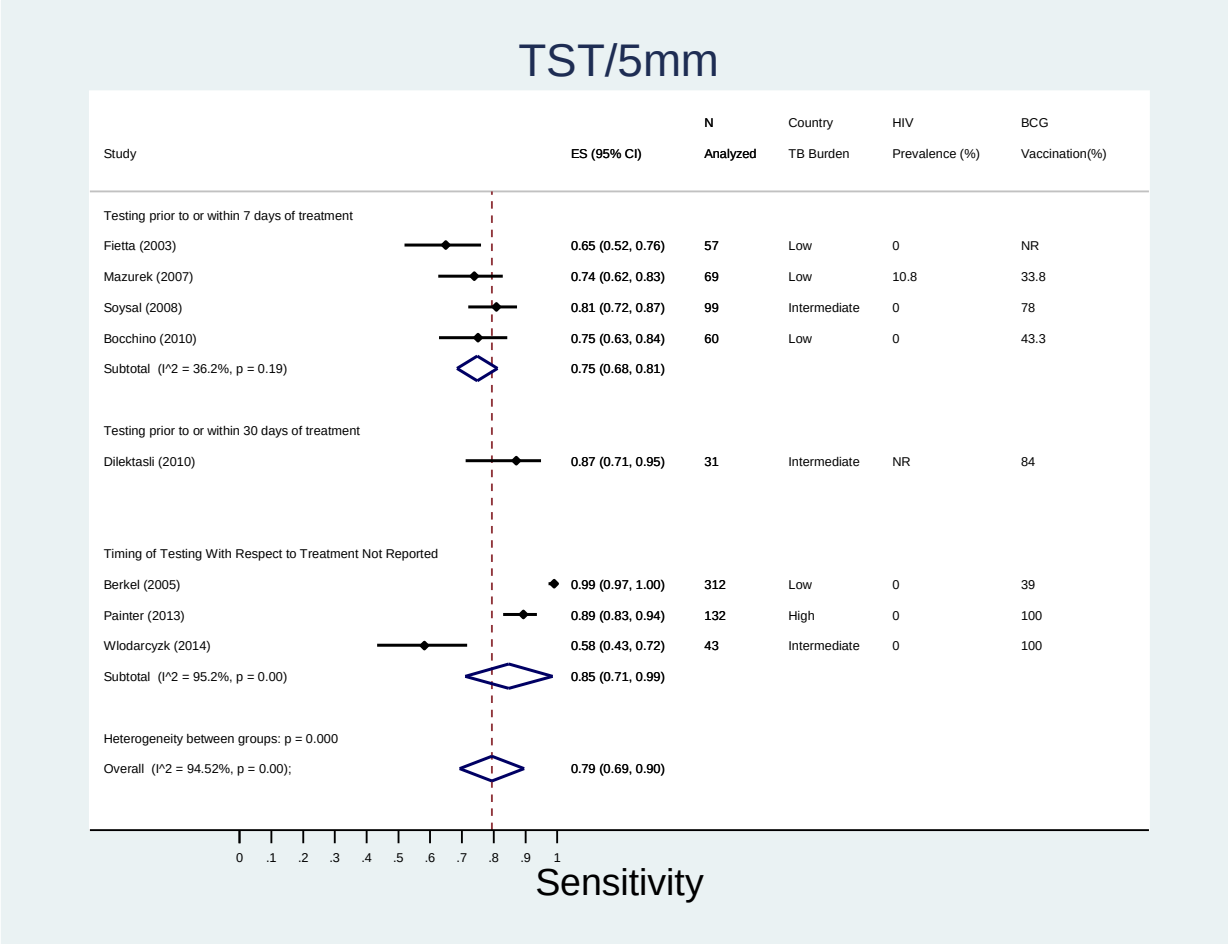
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 6. Specificity for Various Thresholds of TST and IGRA Tests for Tuberculosis Infection Using Maximum Likelihood Random-Effects Model



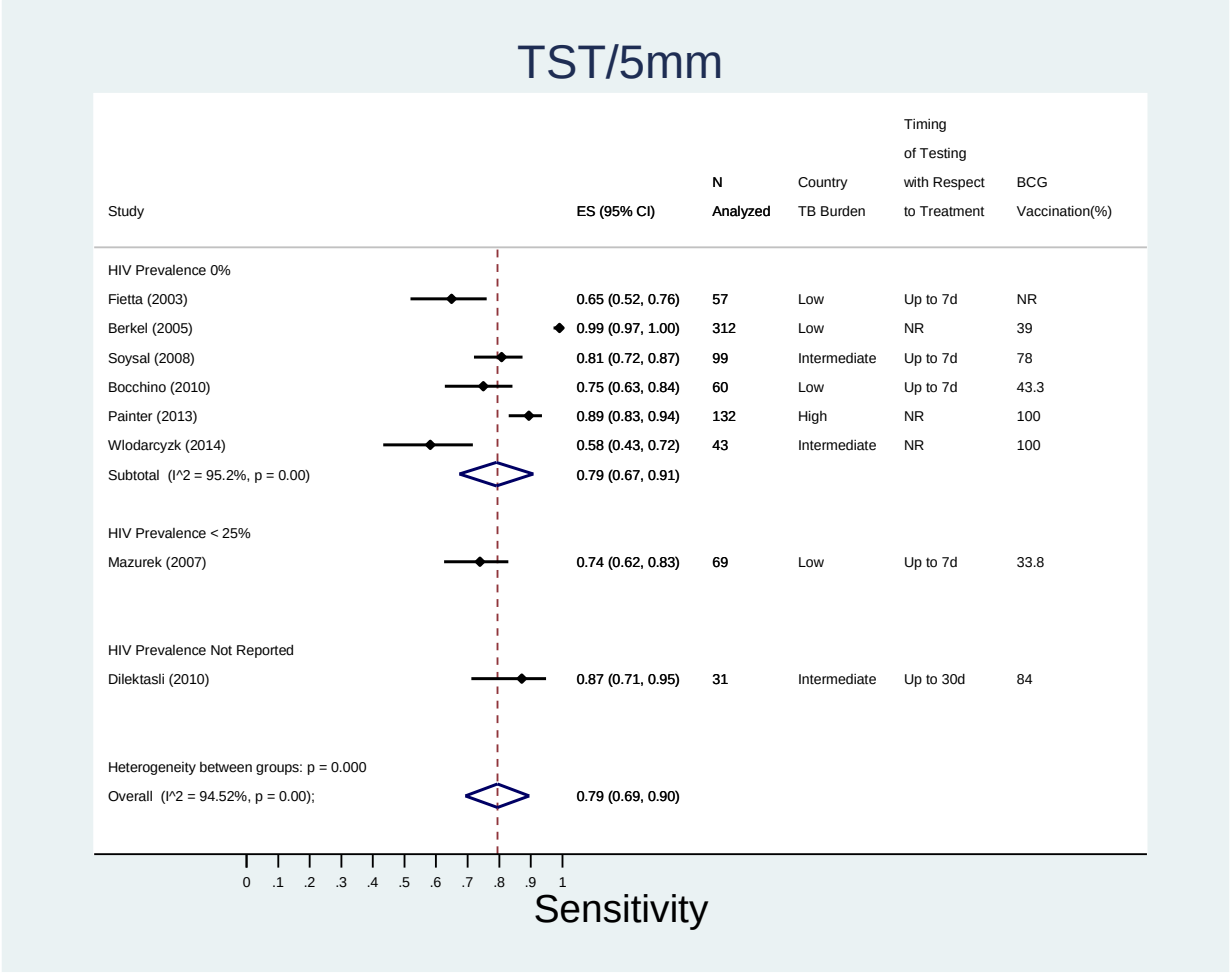
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 7. Sensitivity for TST at 5-mm Threshold, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



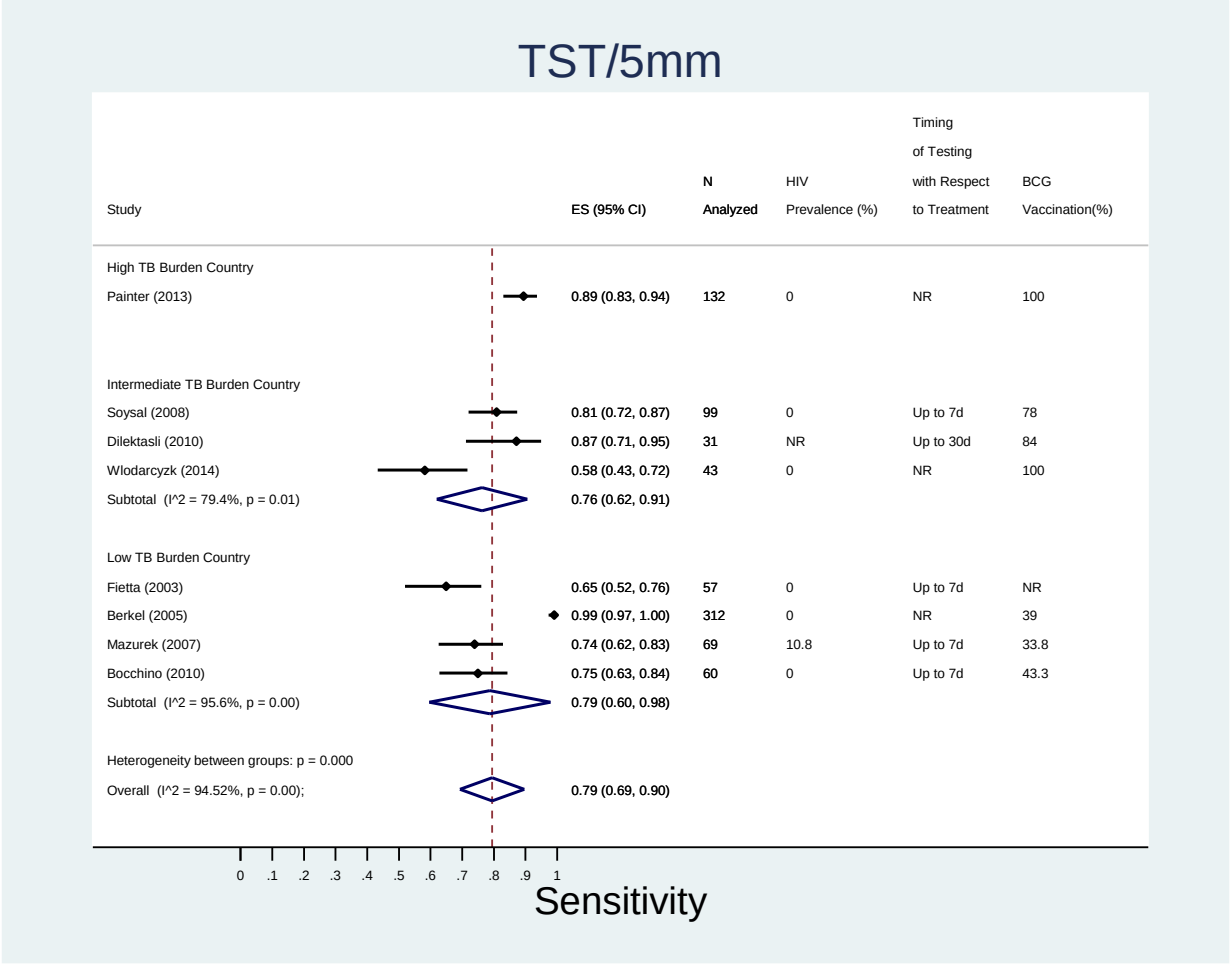
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; HIV=human immunodeficiency virus; NR=not reported; TB=tuberculosis.

Appendix F Figure 8. Sensitivity for TST at 5-mm Threshold, Stratified by HIV Prevalence of the Study Population



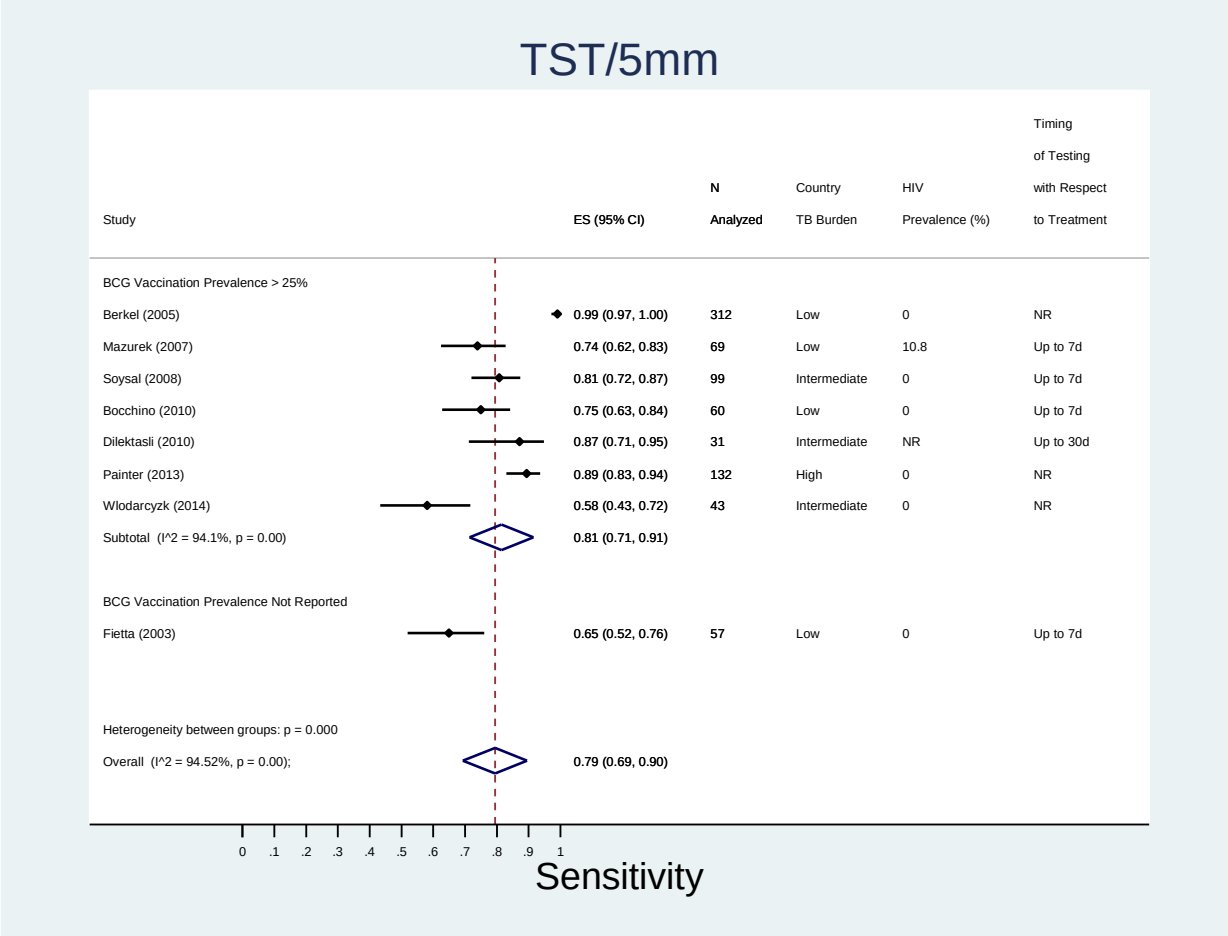
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 9. Sensitivity for TST at 5-mm Threshold, Stratified by Country TB Burden of the Study Setting



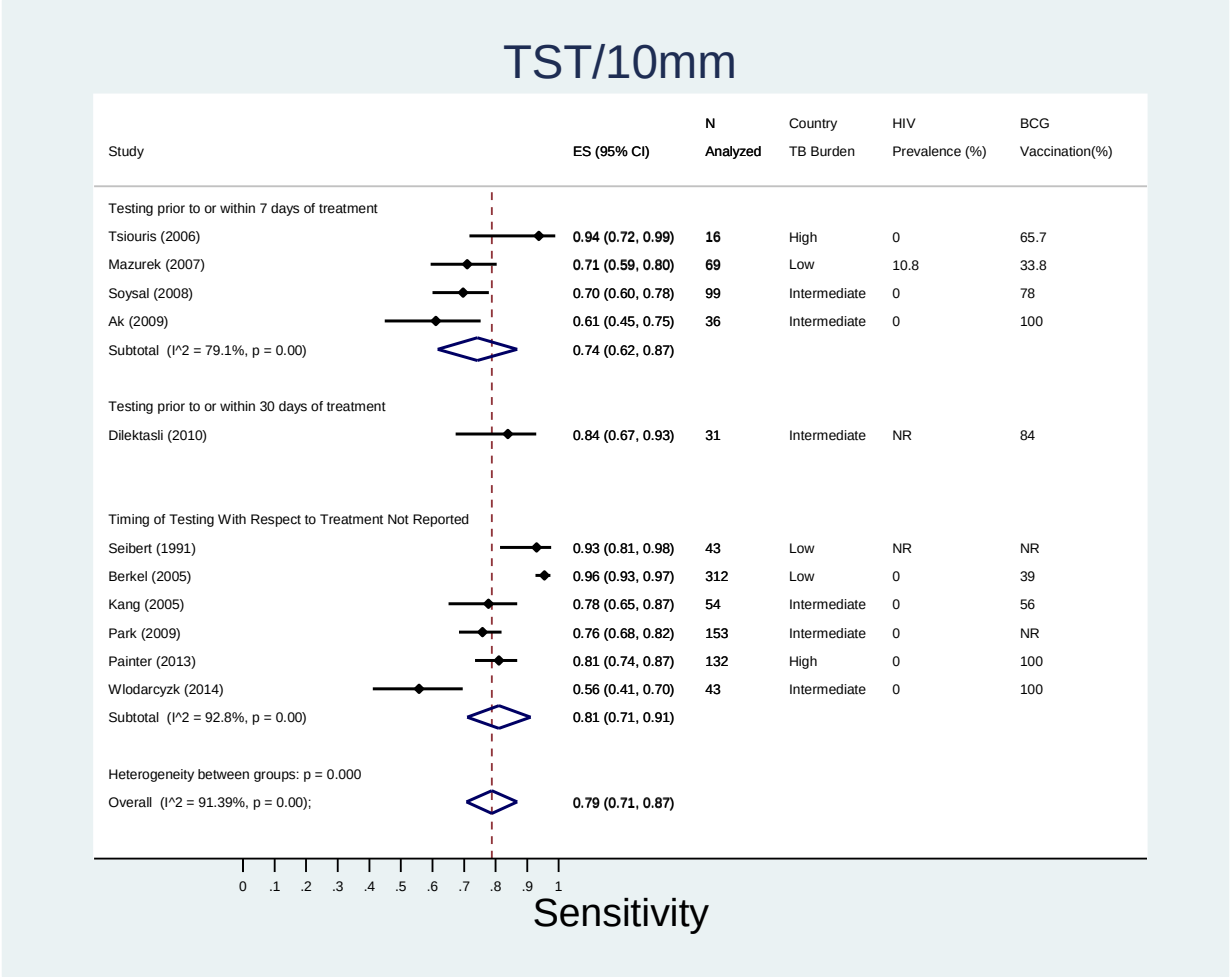
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 10. Sensitivity for TST at 5-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Population



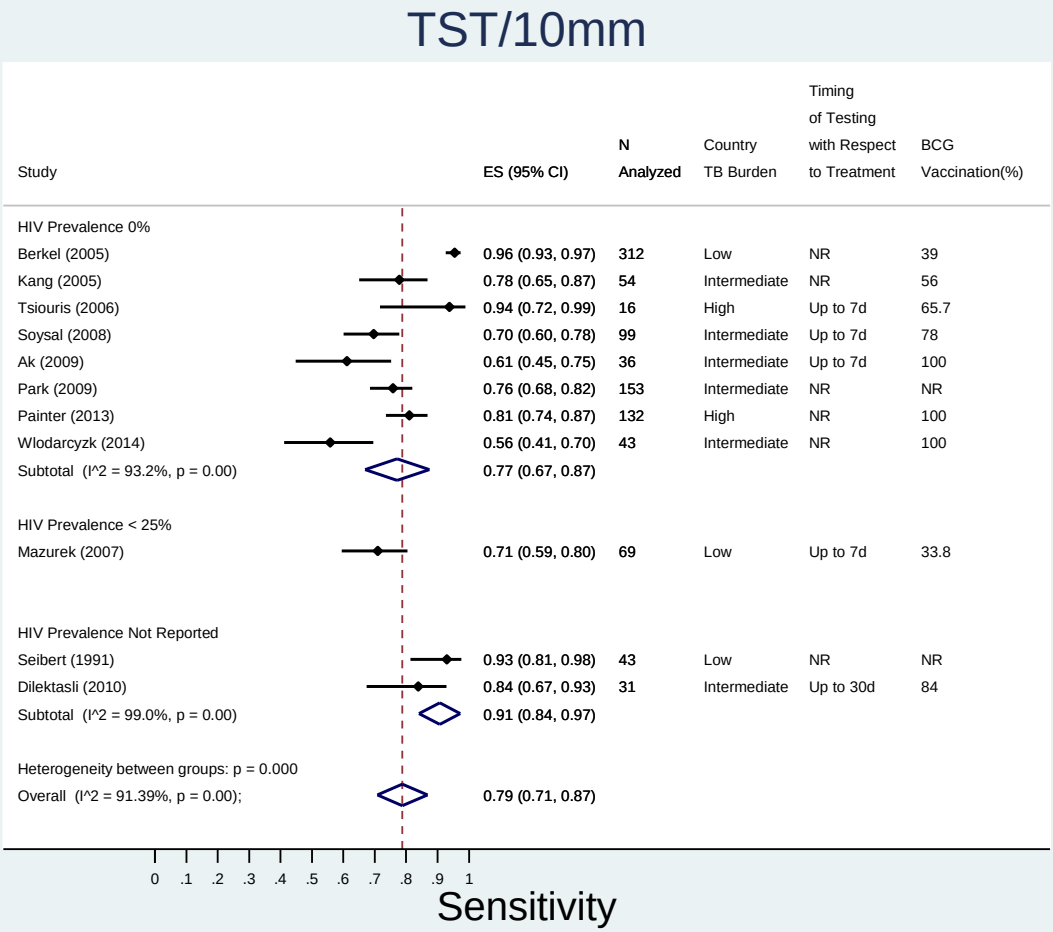
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 11. Sensitivity for TST at 10-mm Threshold, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



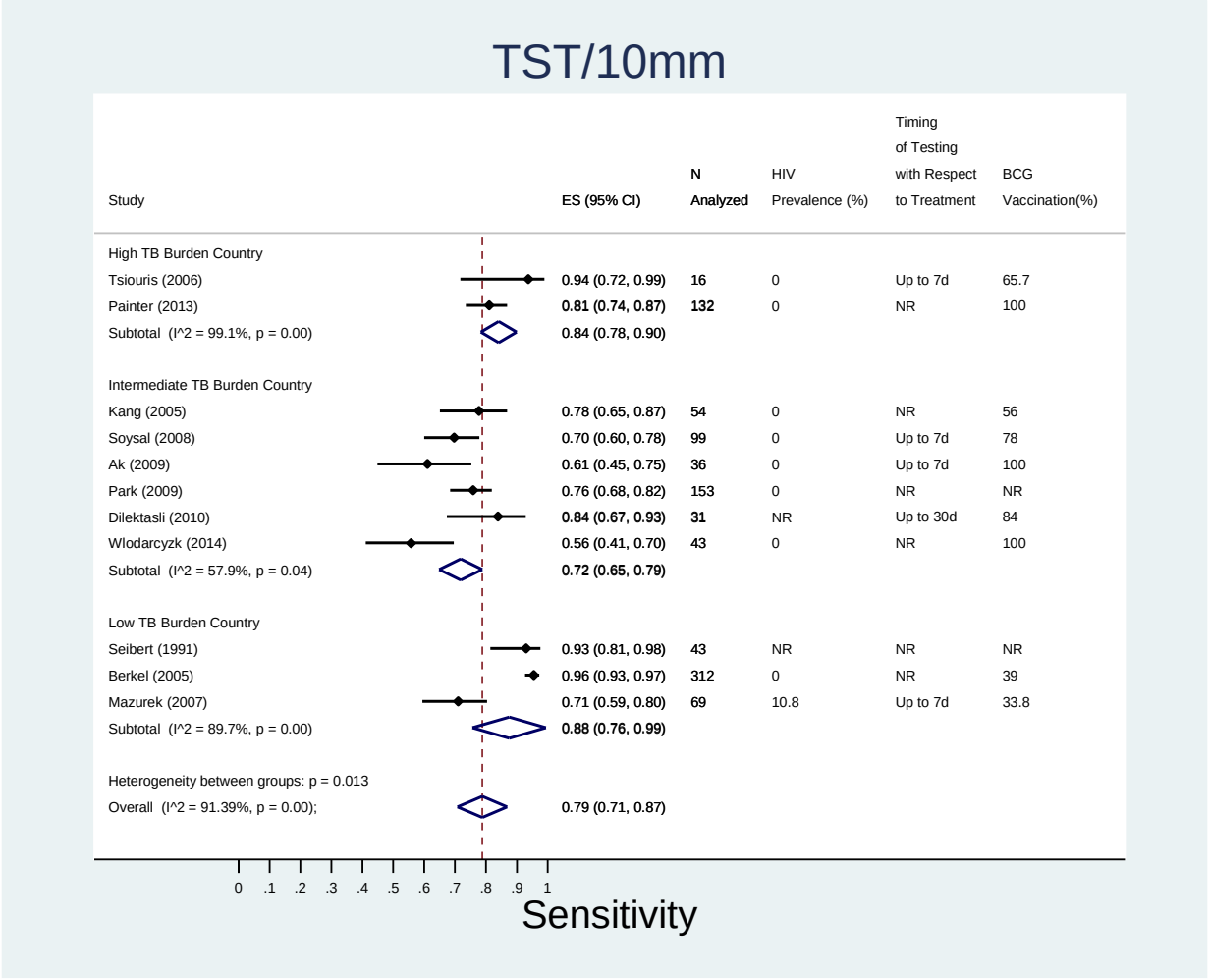
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 12. Sensitivity for TST at 10-mm Threshold, Stratified by HIV Prevalence of the Study Population



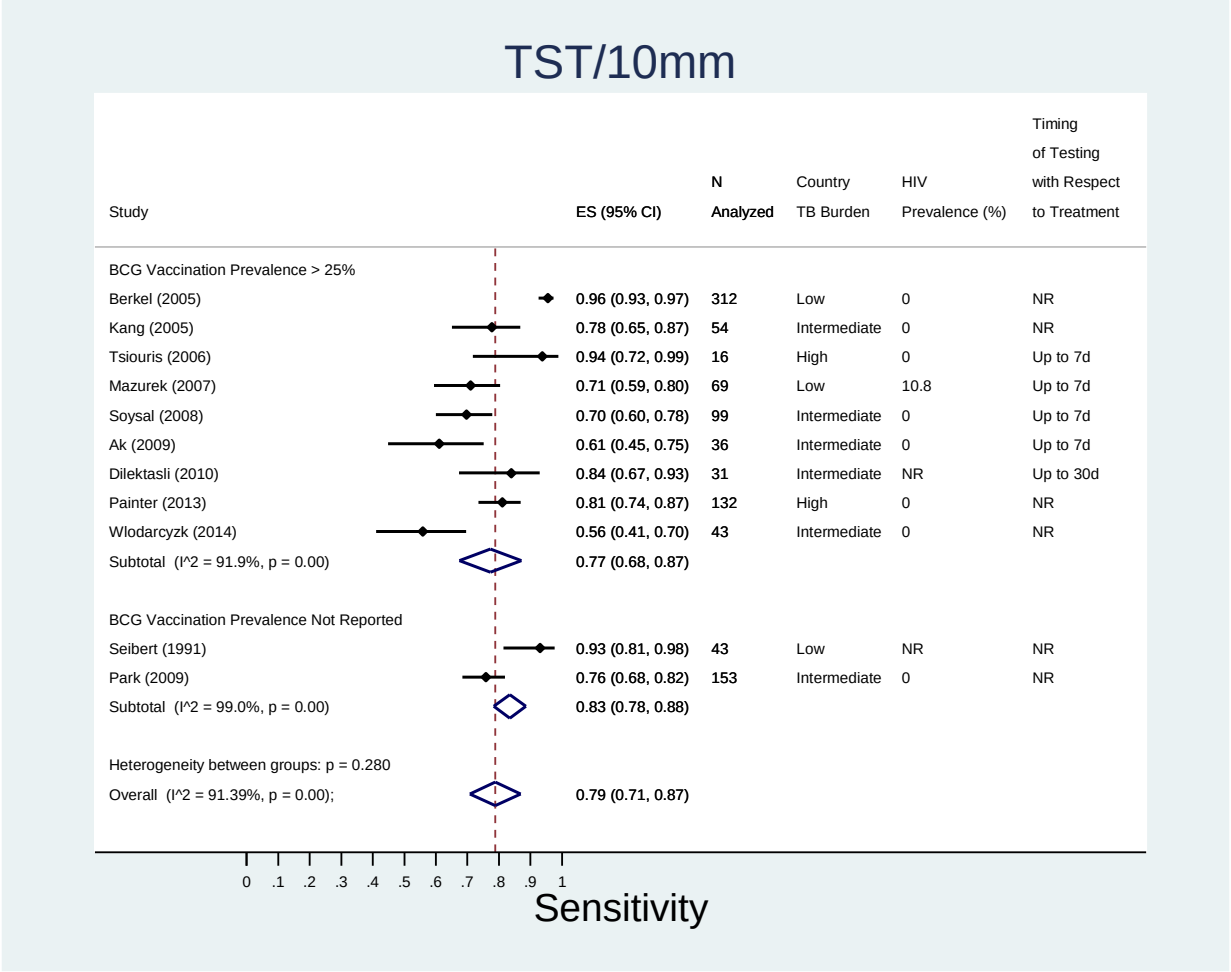
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 13. Sensitivity for TST at 10-mm Threshold, Stratified by Country TB Burden of the Study Setting



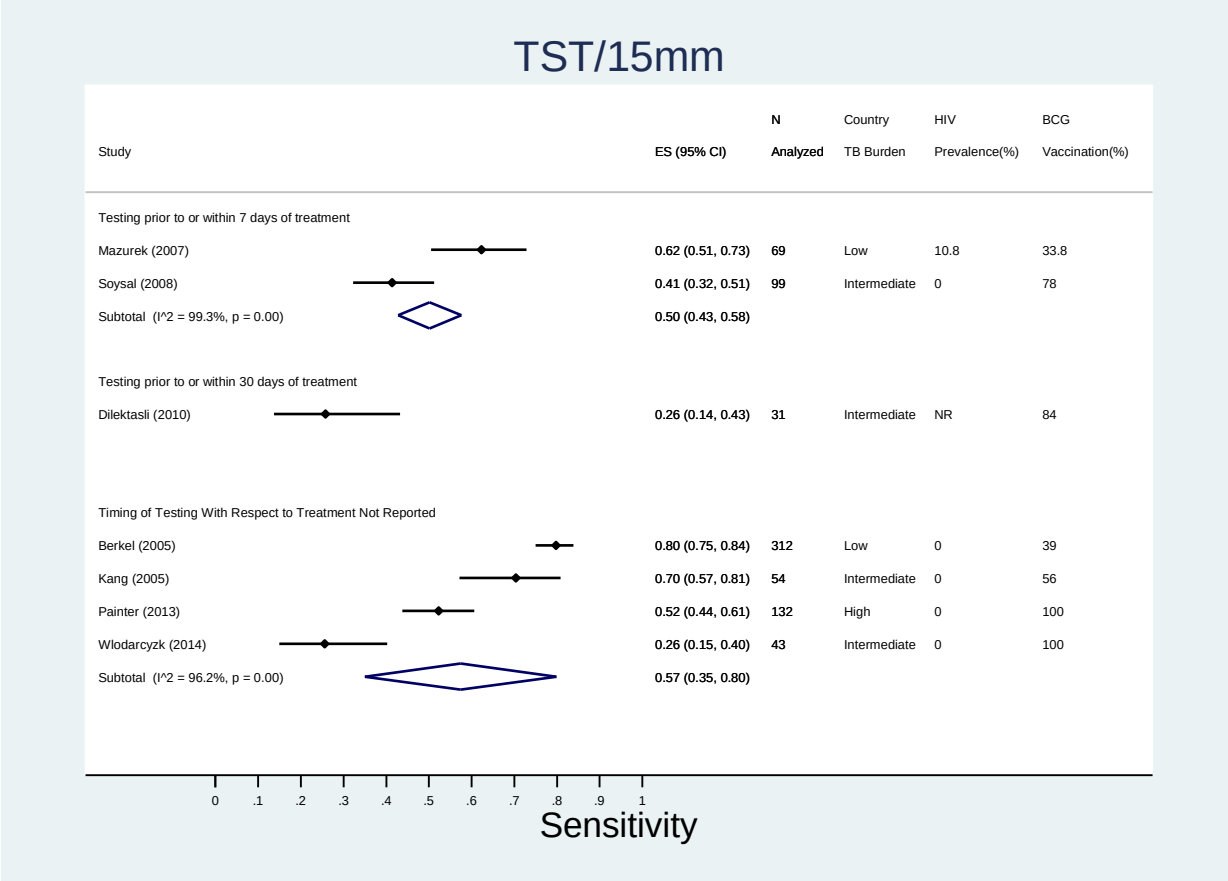
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; mm=millimeter; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 14. Sensitivity for TST at 10-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Setting



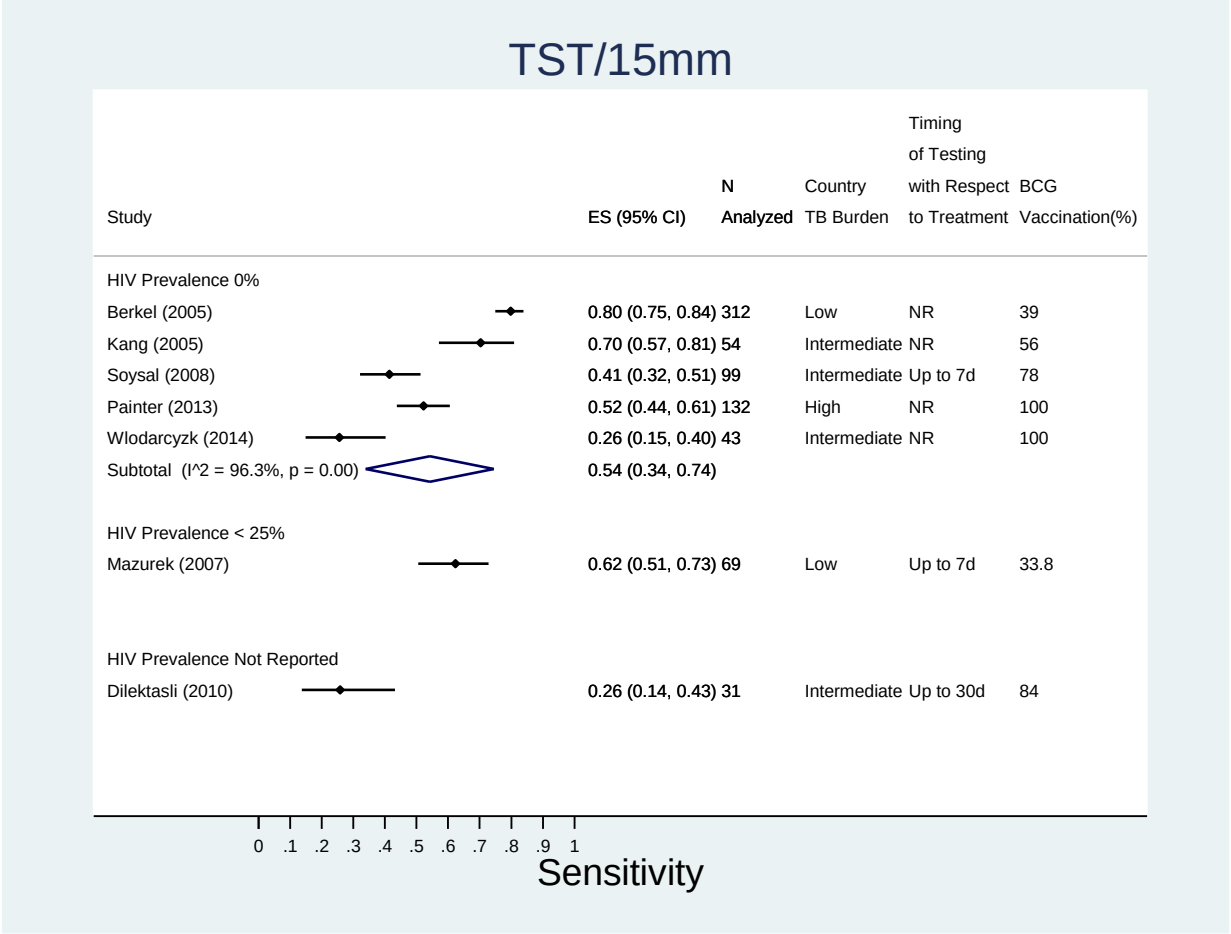
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 15. Sensitivity for TST at 15-mm Threshold, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



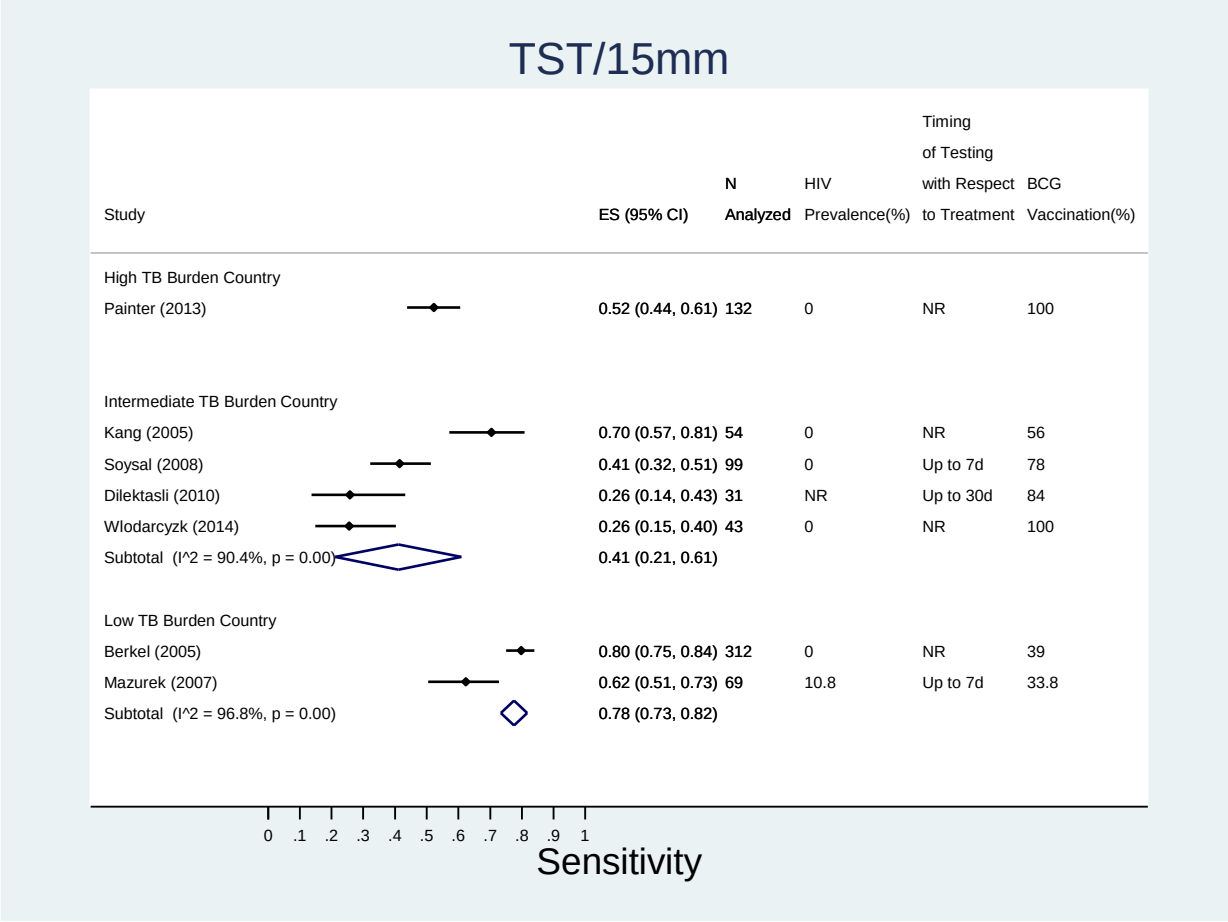
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 16. Sensitivity for TST at 15-mm Threshold, Stratified by HIV Prevalence of the Study Population



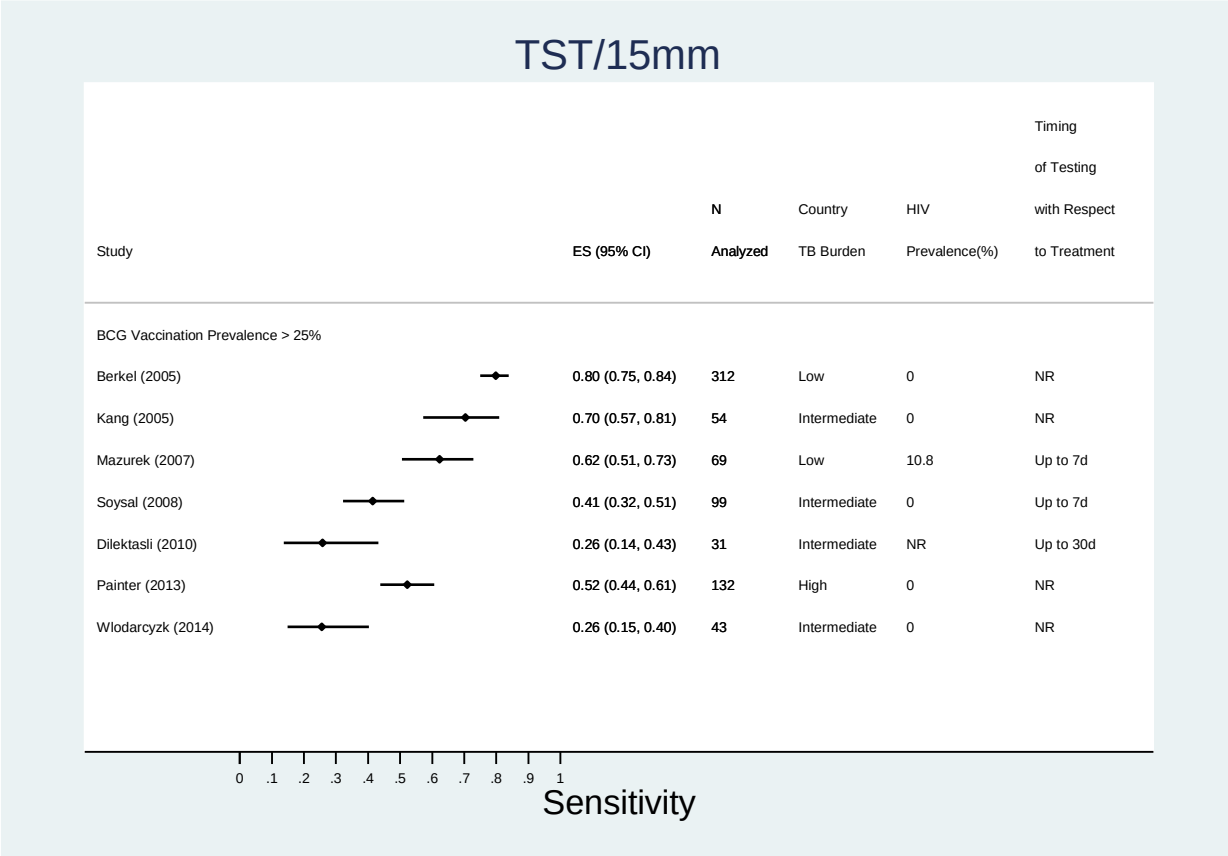
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 17. Sensitivity for TST at 15-mm Threshold, Stratified by Country TB Burden of the Study Setting



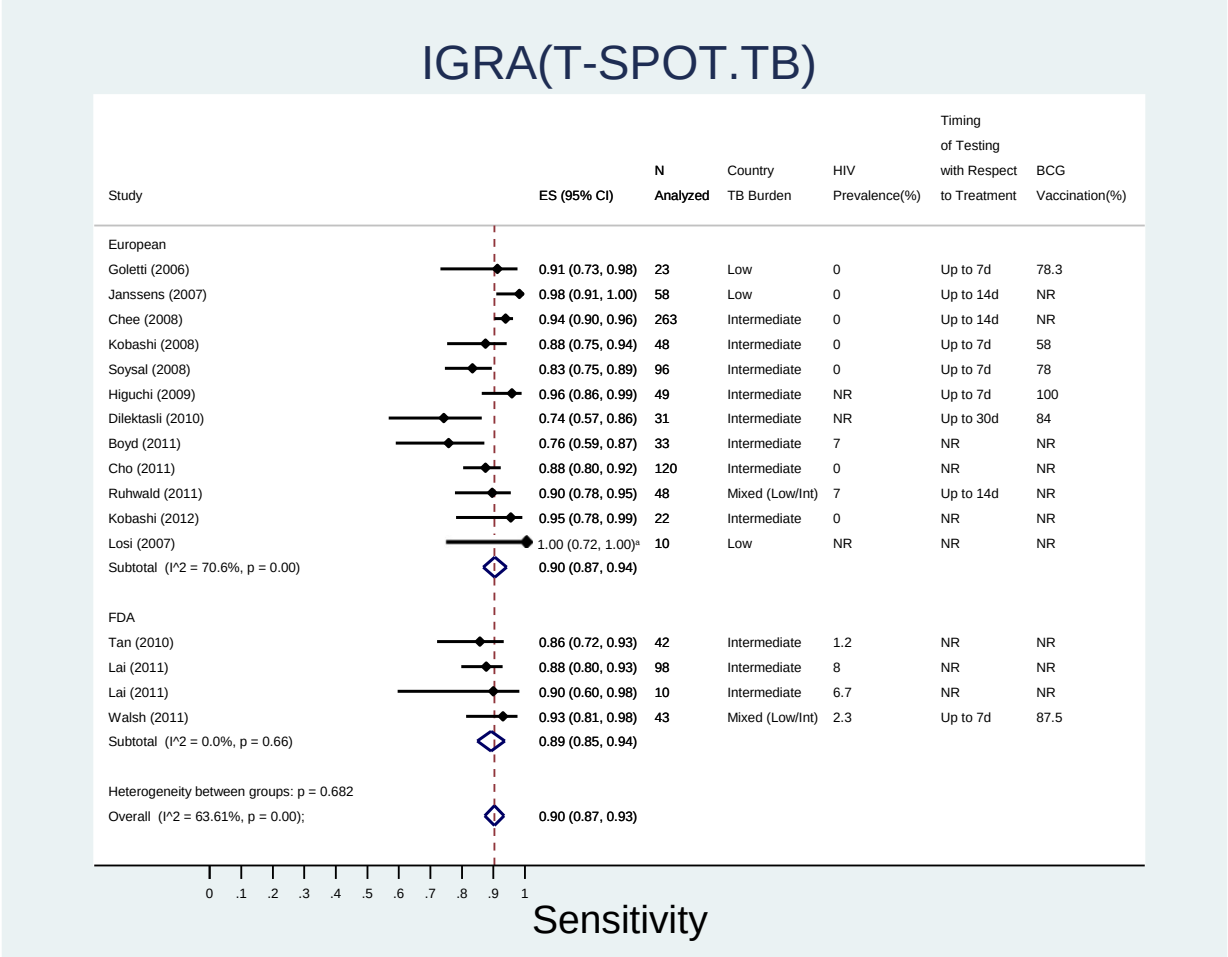
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 18. Sensitivity for TST at 15-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Population



Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

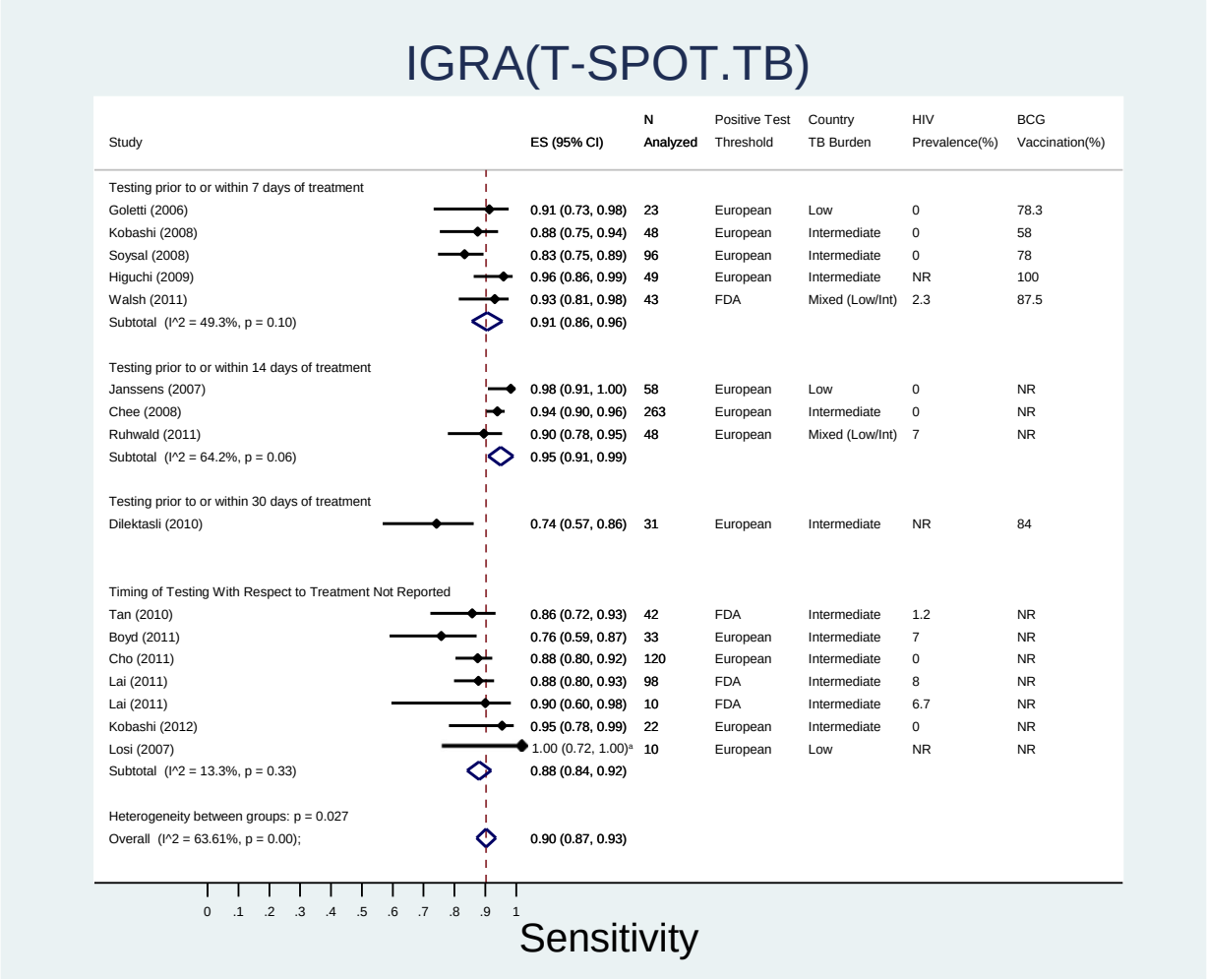
Appendix F Figure 19. Sensitivity of T-SPOT.*TB* Test, Stratified by Threshold Used for Positive Test



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

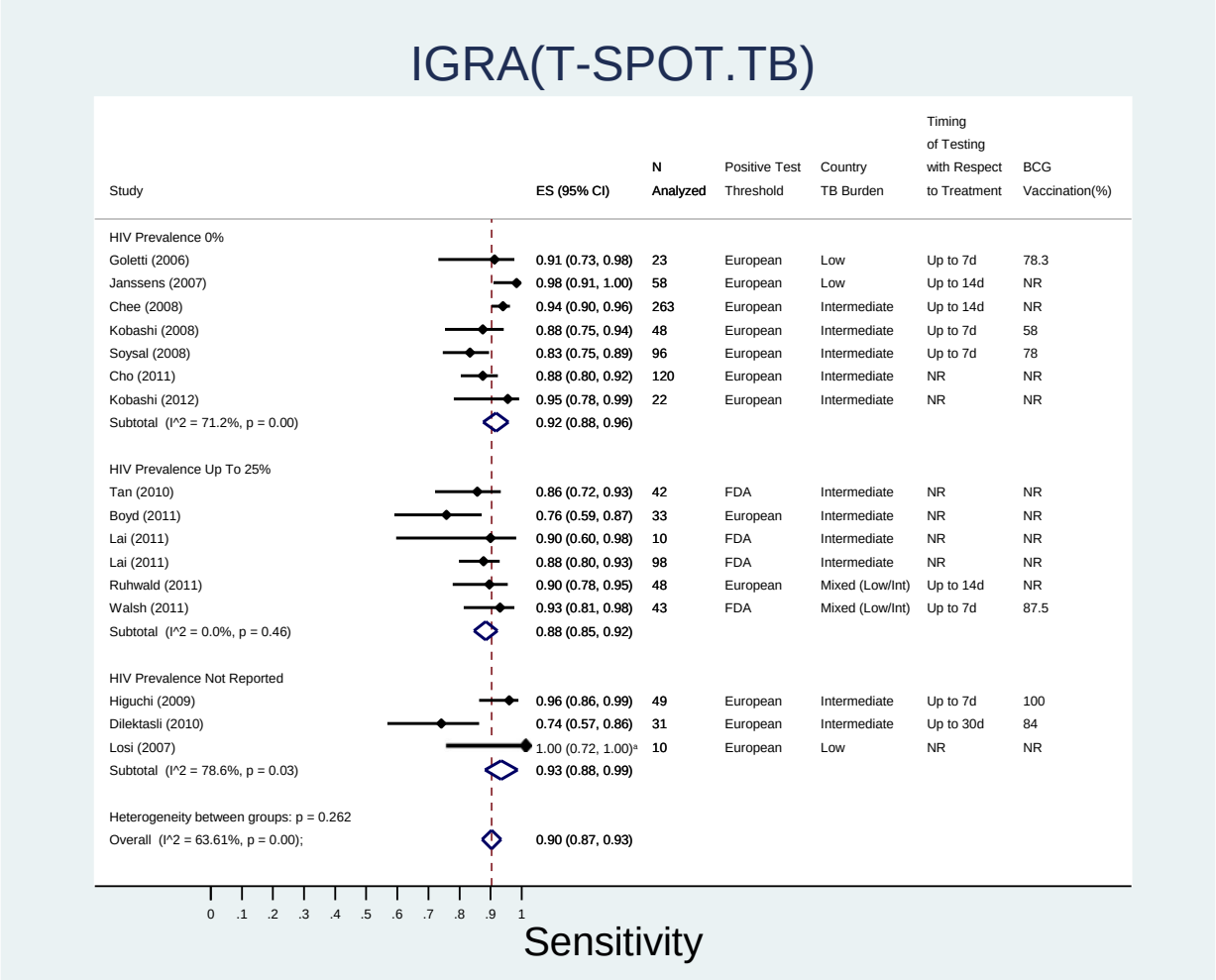
Appendix F Figure 20. Sensitivity of T-SPOT.*TB* Test, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; FDA=U.S. Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

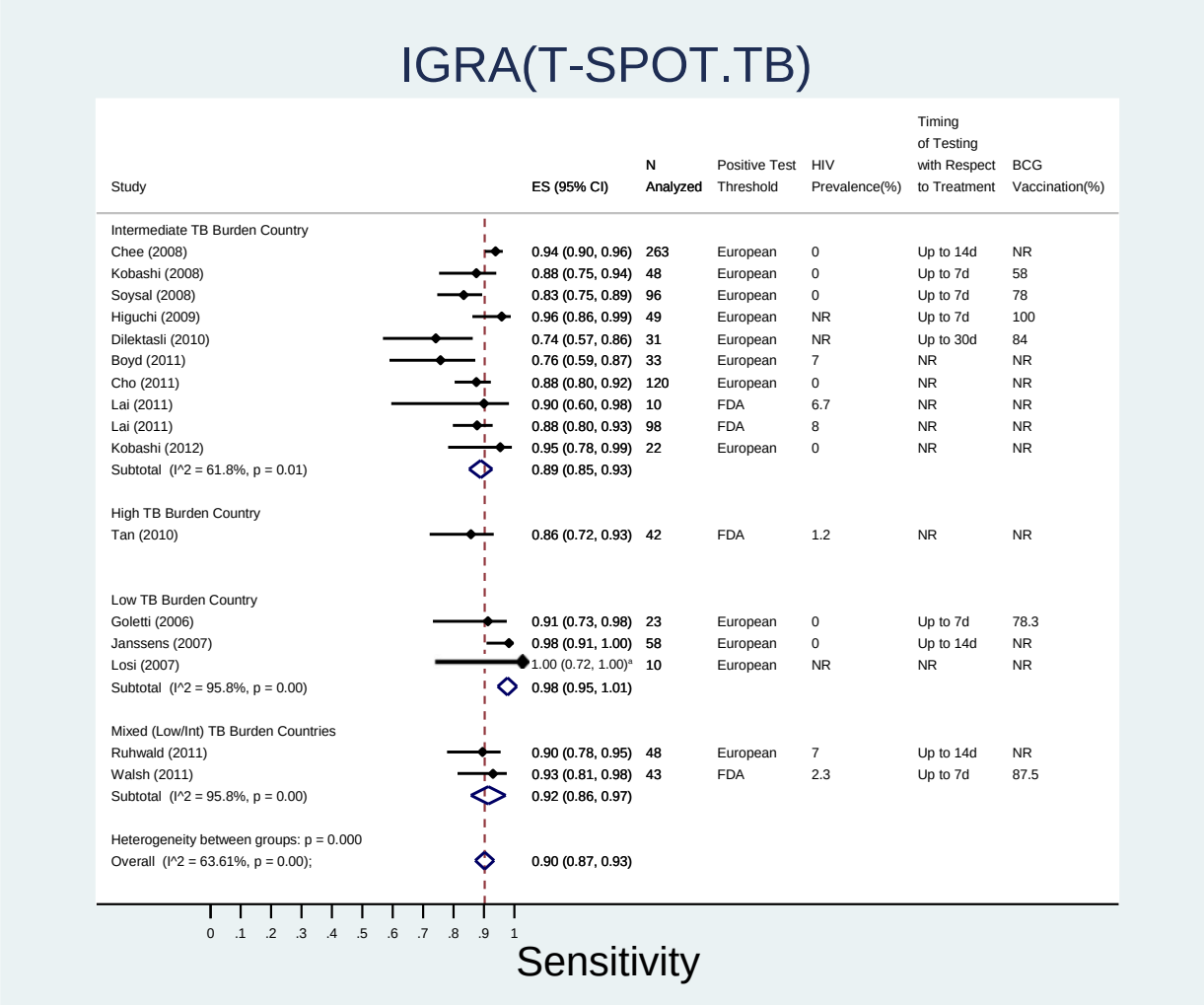
Appendix F Figure 21. Sensitivity of T-SPOT.*TB* Test, Stratified by HIV Prevalence of the Study Population



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; FDA=U.S. Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

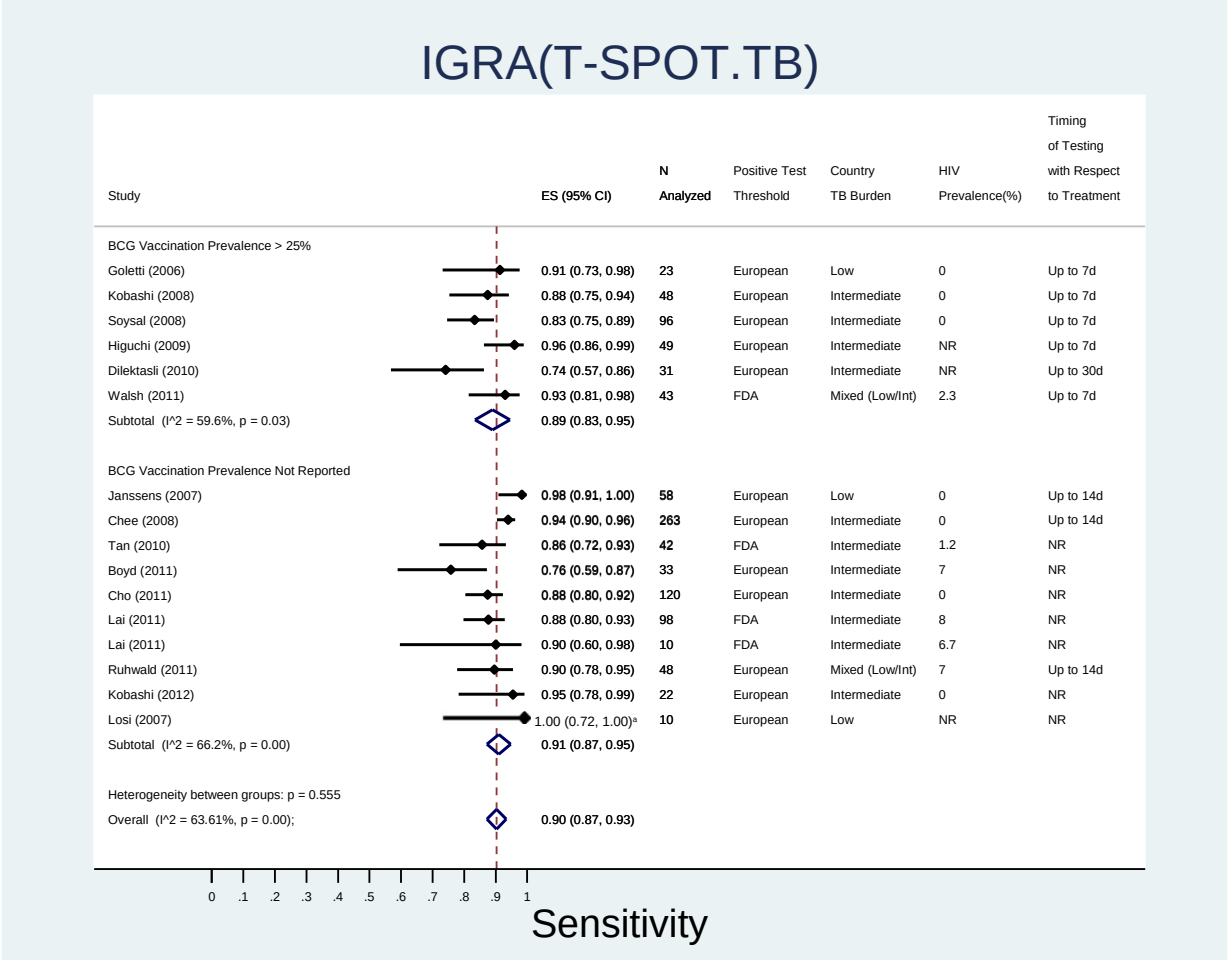
Appendix F Figure 22. Sensitivity of T-SPOT.*TB* Test, Stratified by Country TB Burden of the Study Setting



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; FDA=U.S. Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

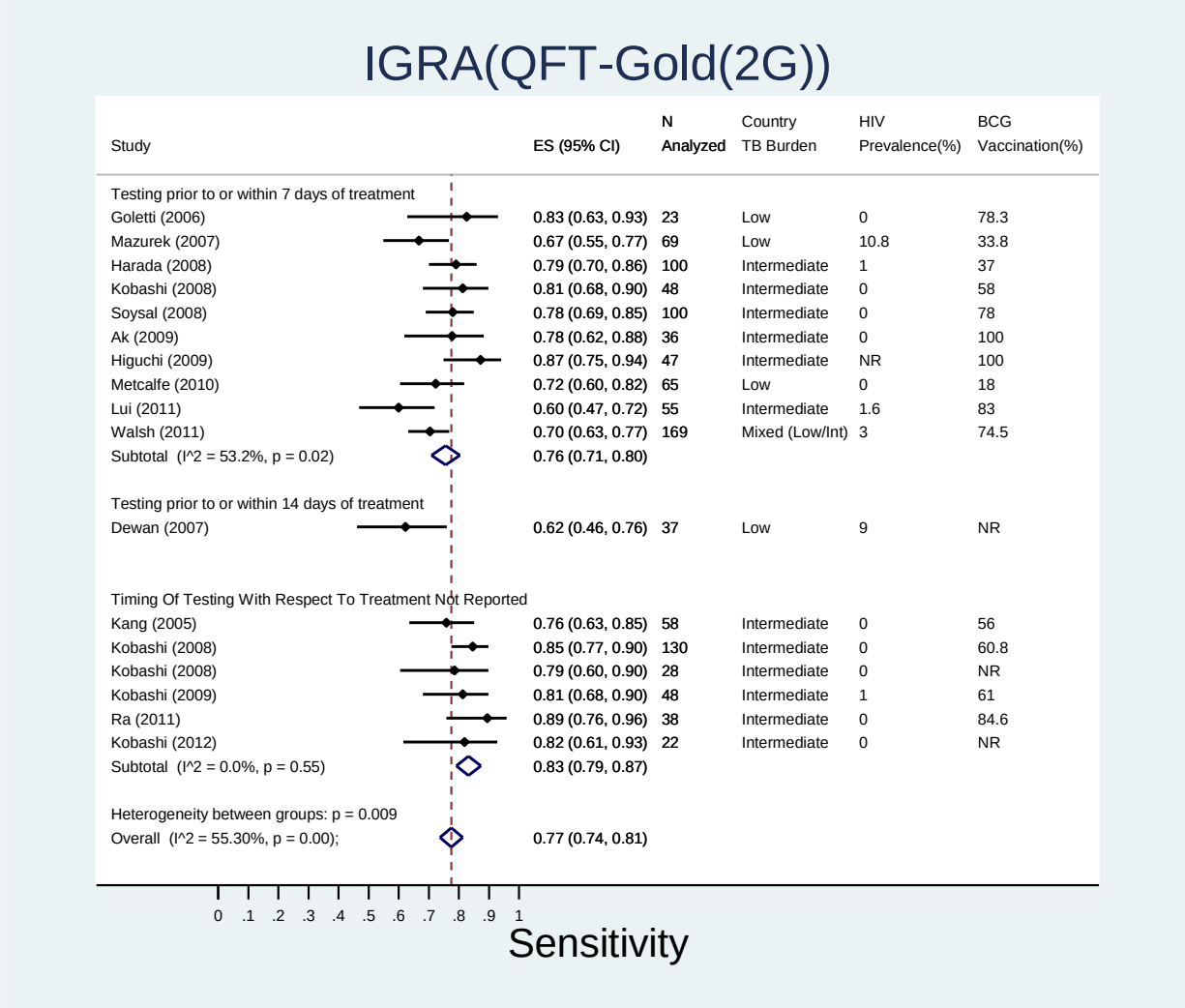
Appendix F Figure 23. Sensitivity of T-SPOT.*TB* Test, Stratified by BCG Vaccination Prevalence of the Study Population



[a] Excluded from pooled estimate due to point estimate of 1.0.

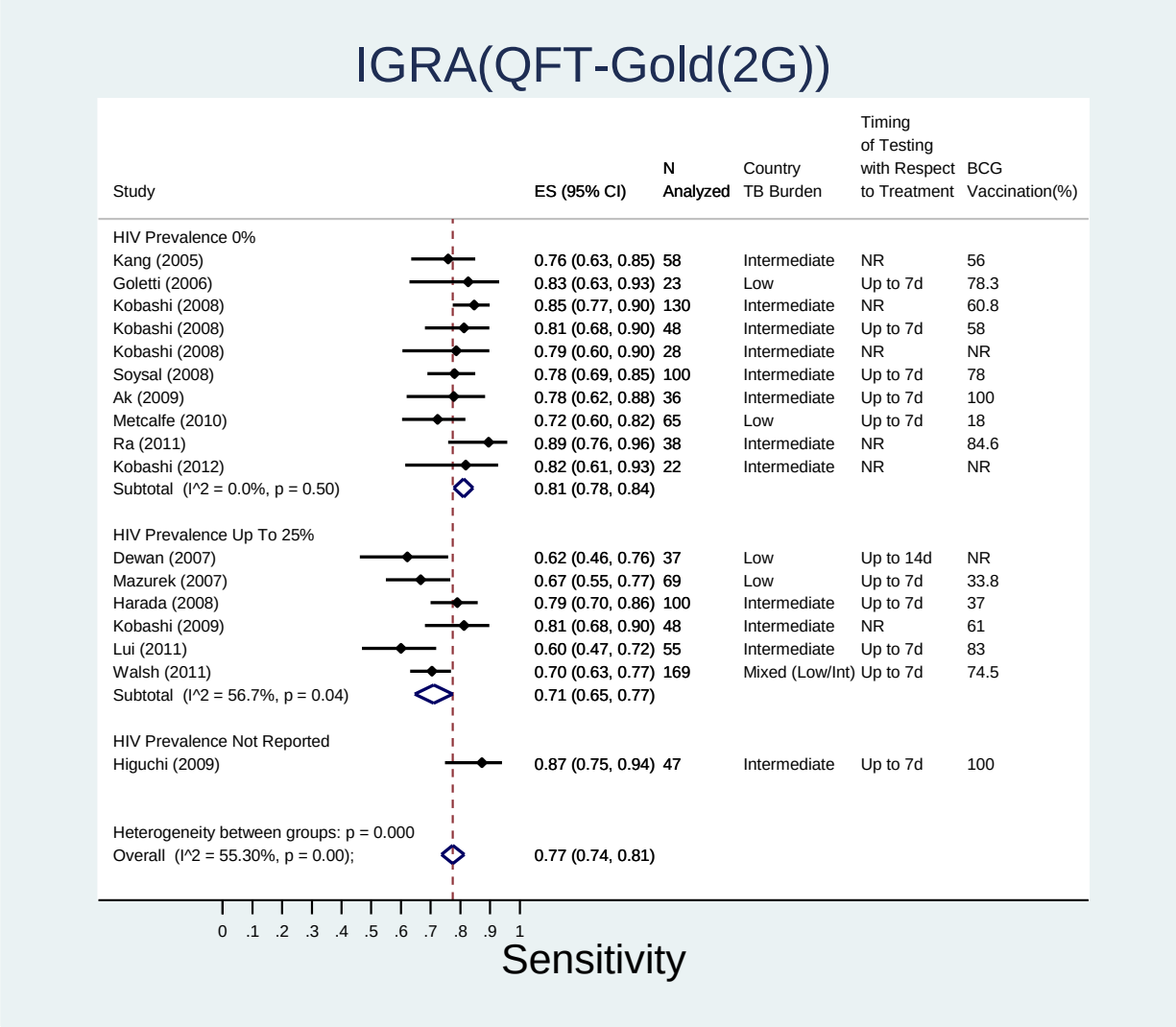
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; FDA=U.S. Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 24. Sensitivity of QFT-Gold (2nd-Generation) Test, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



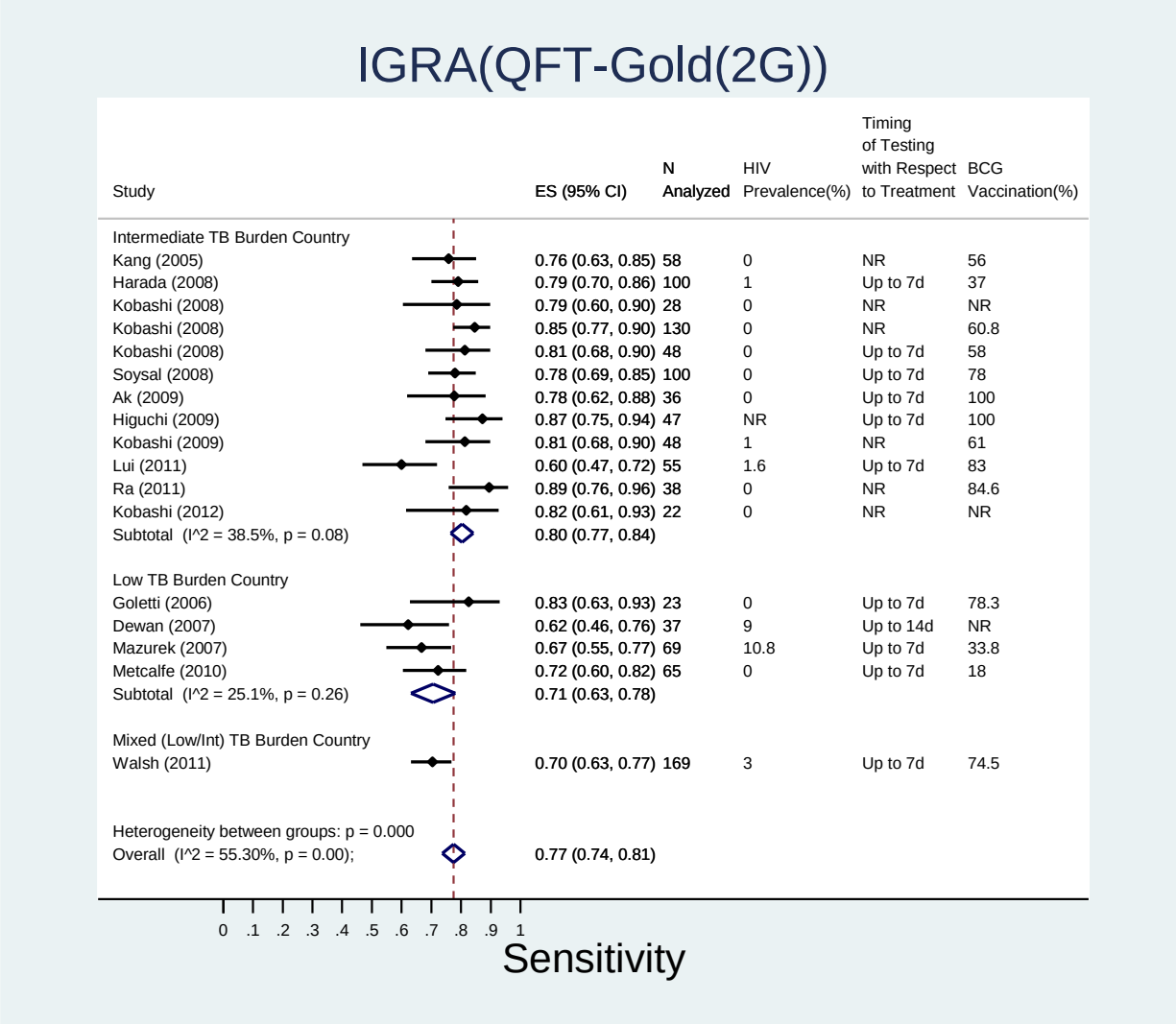
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 25. Sensitivity of QFT-Gold (2nd-Generation) Test, Stratified by HIV Prevalence of the Study Population



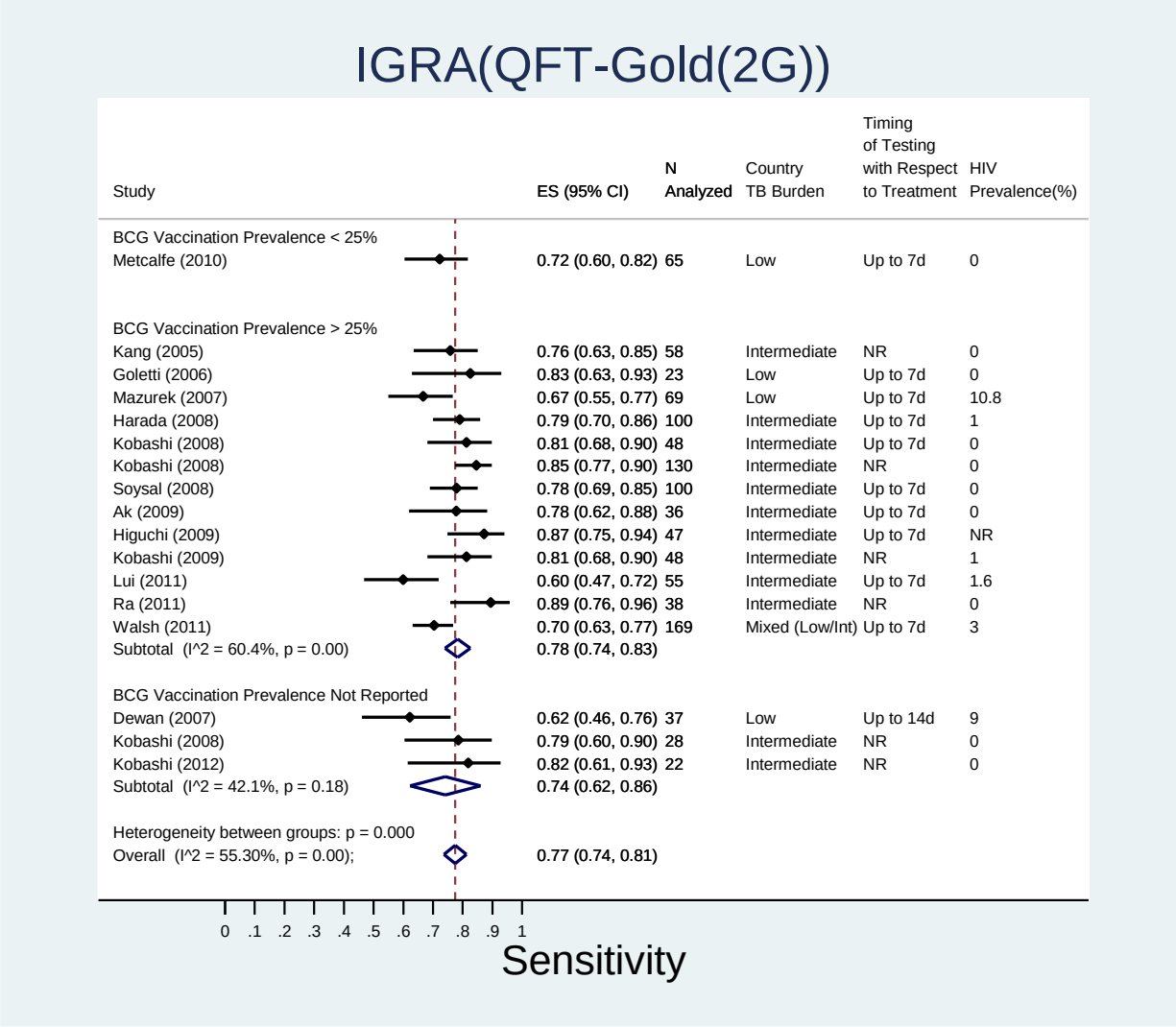
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported.

Appendix F Figure 26. Sensitivity of QFT-Gold (2nd-Generation) Test, Stratified by Country TB Burden of the Study Setting



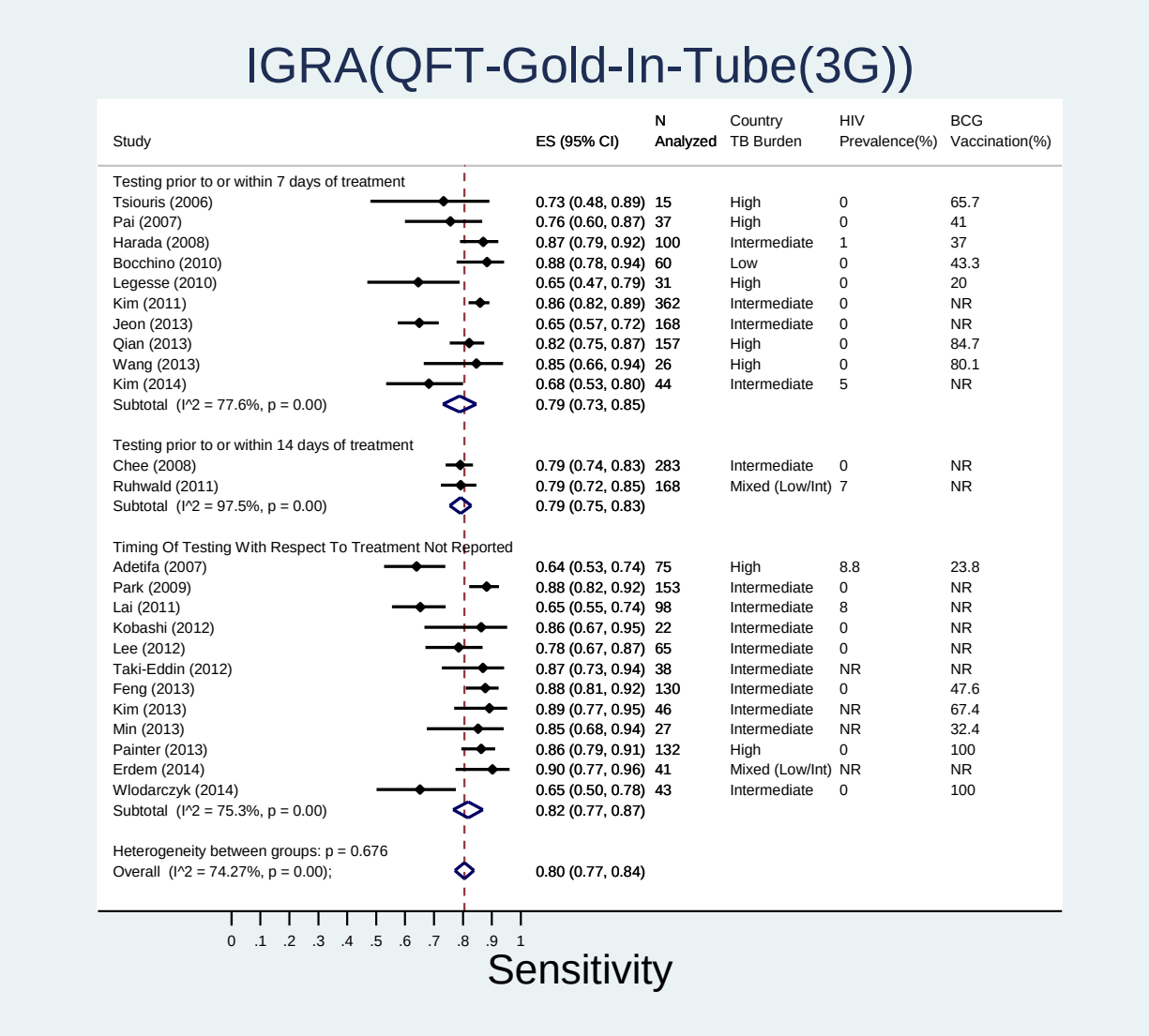
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 27. Sensitivity of QFT-Gold (2nd-Generation) Test, Stratified by BCG Vaccination Prevalence of the Study Population



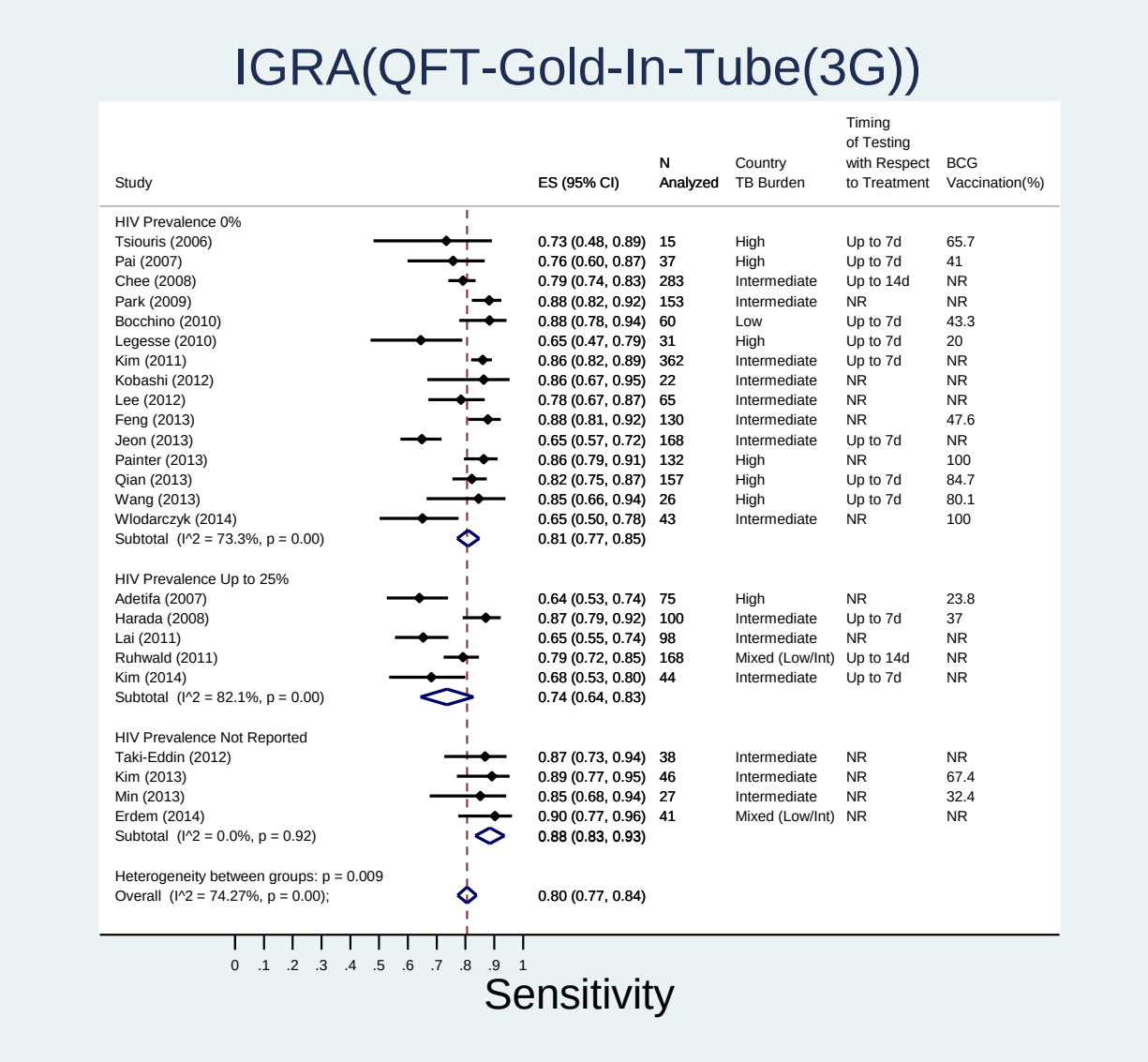
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 28. Sensitivity of QFT-Gold In-Tube (3rd-Generation) Test, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



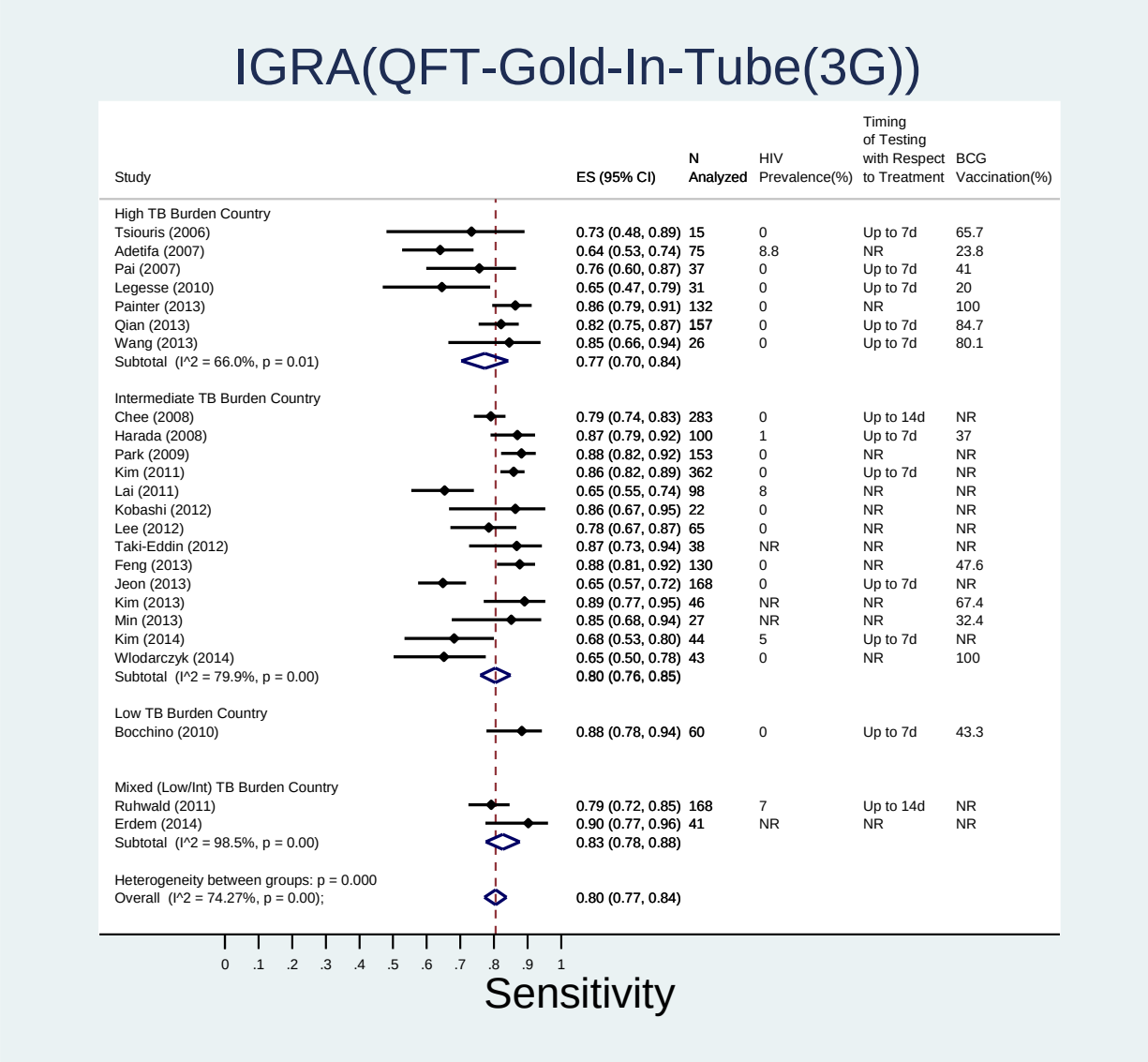
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 29. Sensitivity of QFT-Gold In-Tube (3rd-Generation) Test, Stratified by HIV Prevalence of the Study Population



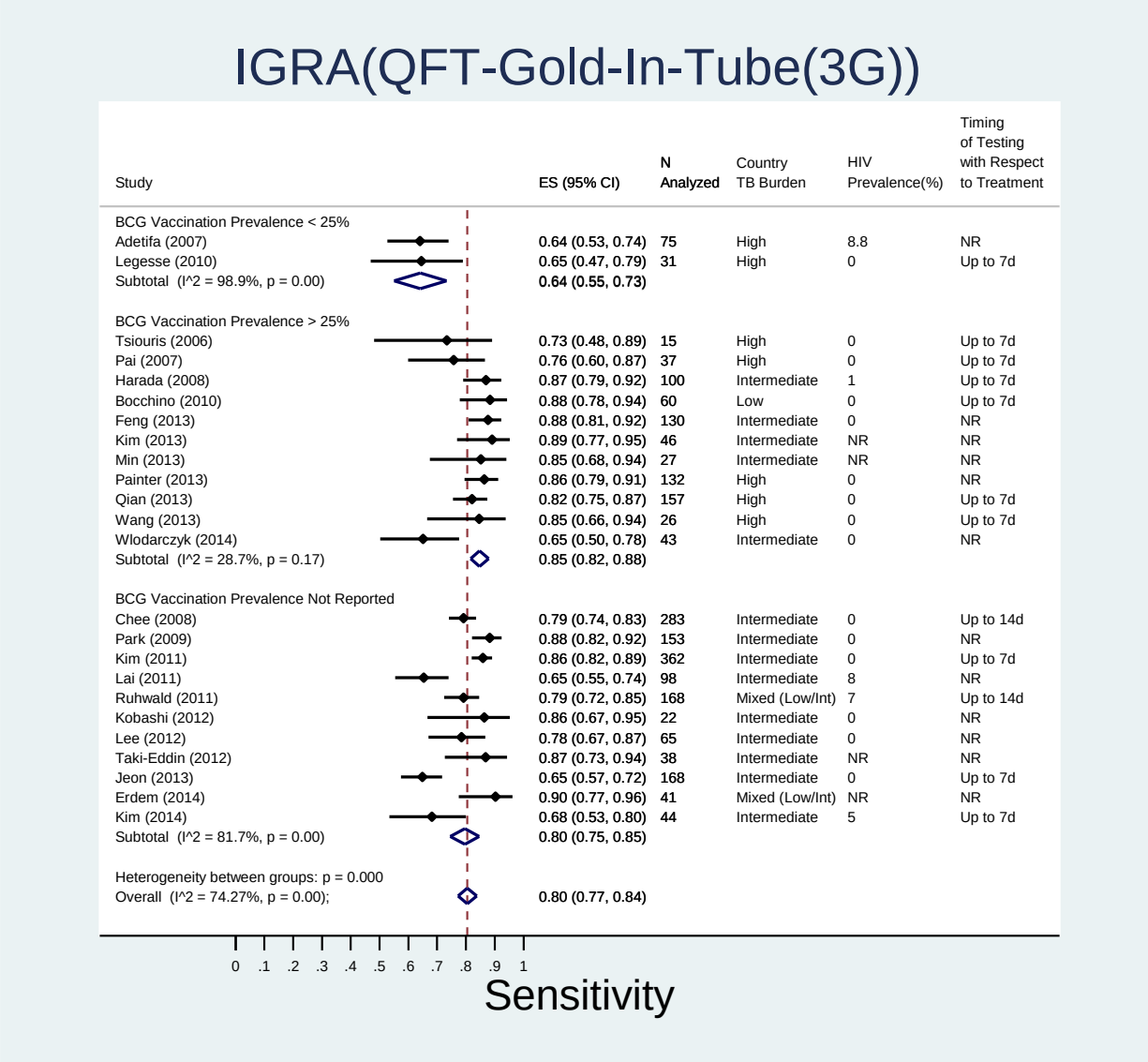
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 30. Sensitivity of QFT-Gold In-Tube (3rd-Generation) Test, Stratified by Country TB Burden of the Study Setting



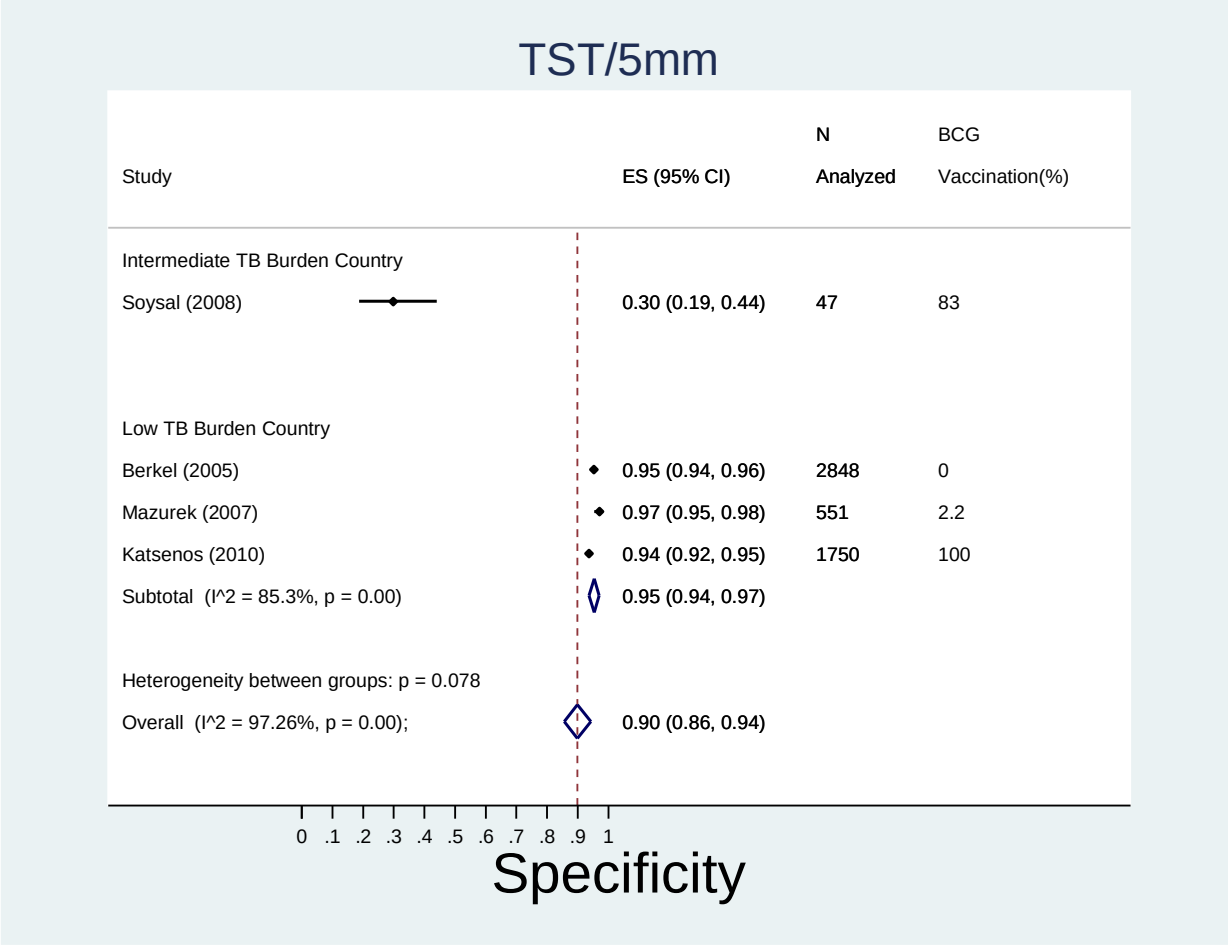
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 31. Sensitivity of QFT-Gold In-Tube (3rd-Generation) Test, Stratified by BCG Vaccination Prevalence of the Study Population



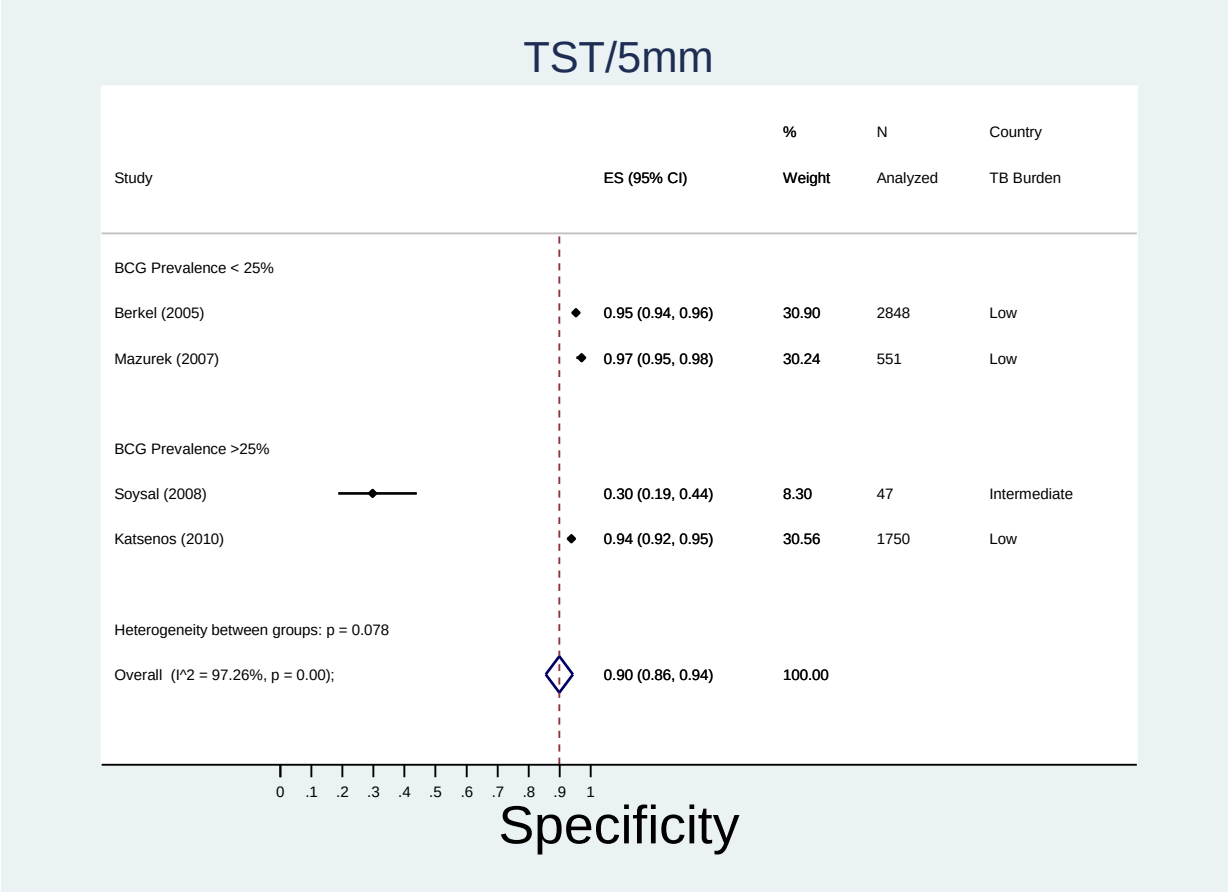
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; d=day; ES=effect size; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 32. Specificity of TST at 5-mm Threshold, Stratified by Country TB Burden of the Study Setting



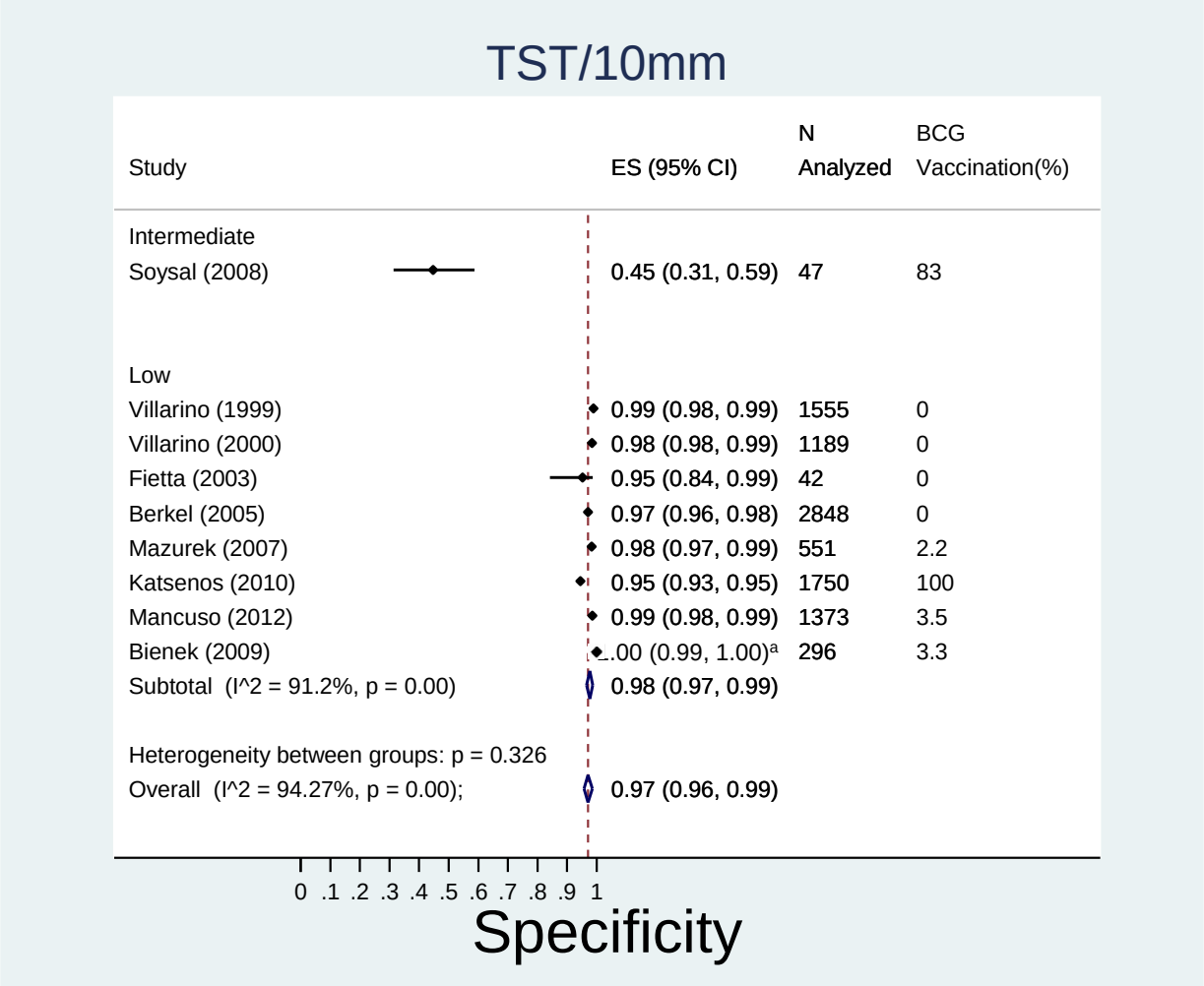
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; N=number; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 33. Specificity of TST at 5-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Population



Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; N=number; TB=tuberculosis; TST=tuberculin skin test.

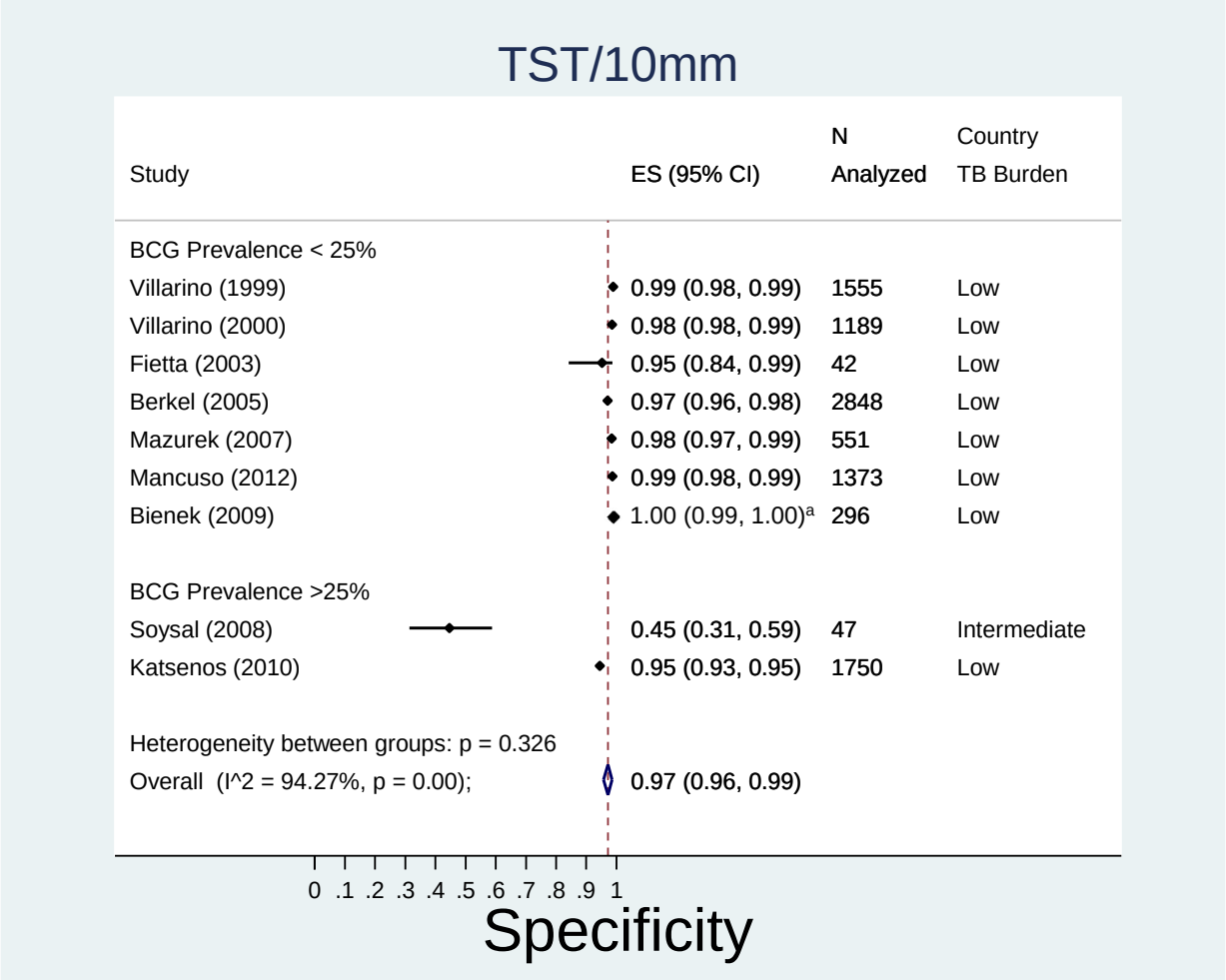
Appendix F Figure 34. Specificity of TST at 10-mm Threshold, Stratified by Country TB Burden of the Study Setting



[a] Excluded from pooled estimate due to point estimate of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; N=number; TB=tuberculosis; TST=tuberculin skin test.

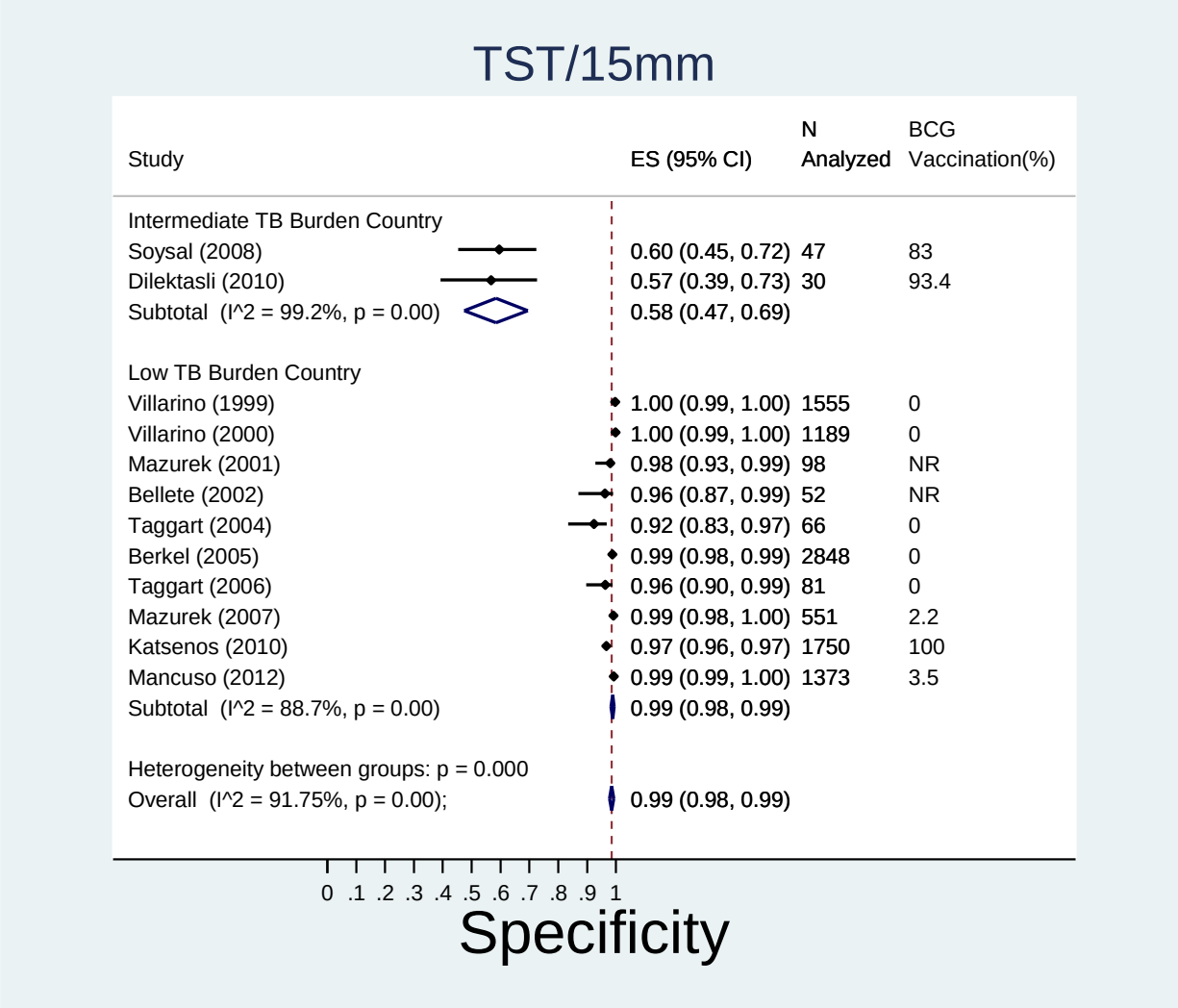
Appendix F Figure 35. Specificity of TST at 10-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Population



[a] Excluded from pooled estimate due to point estimate of 1.0.

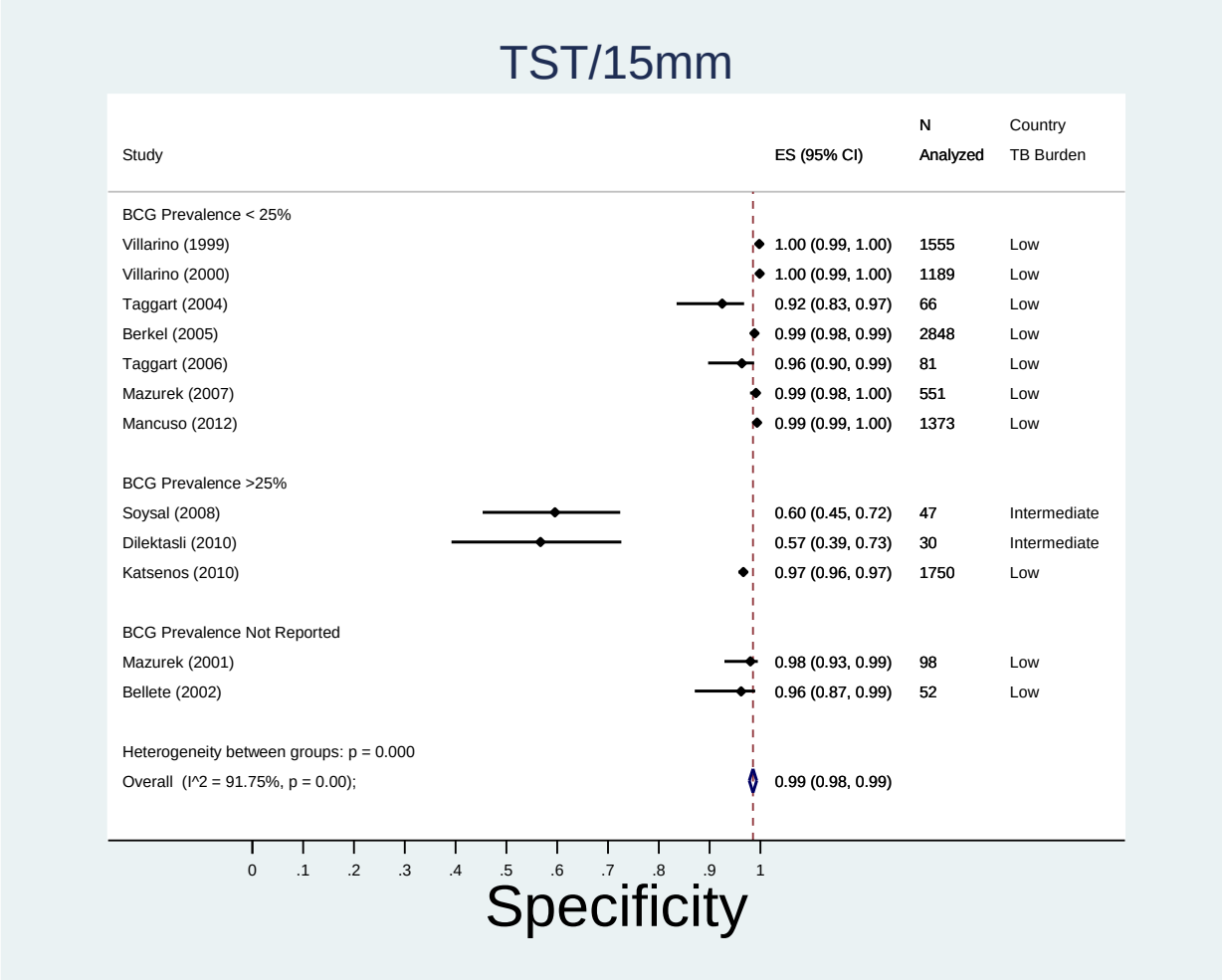
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; N=number; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 36. Specificity of TST at 15-mm Threshold, Stratified by Country TB Burden of the Study Setting



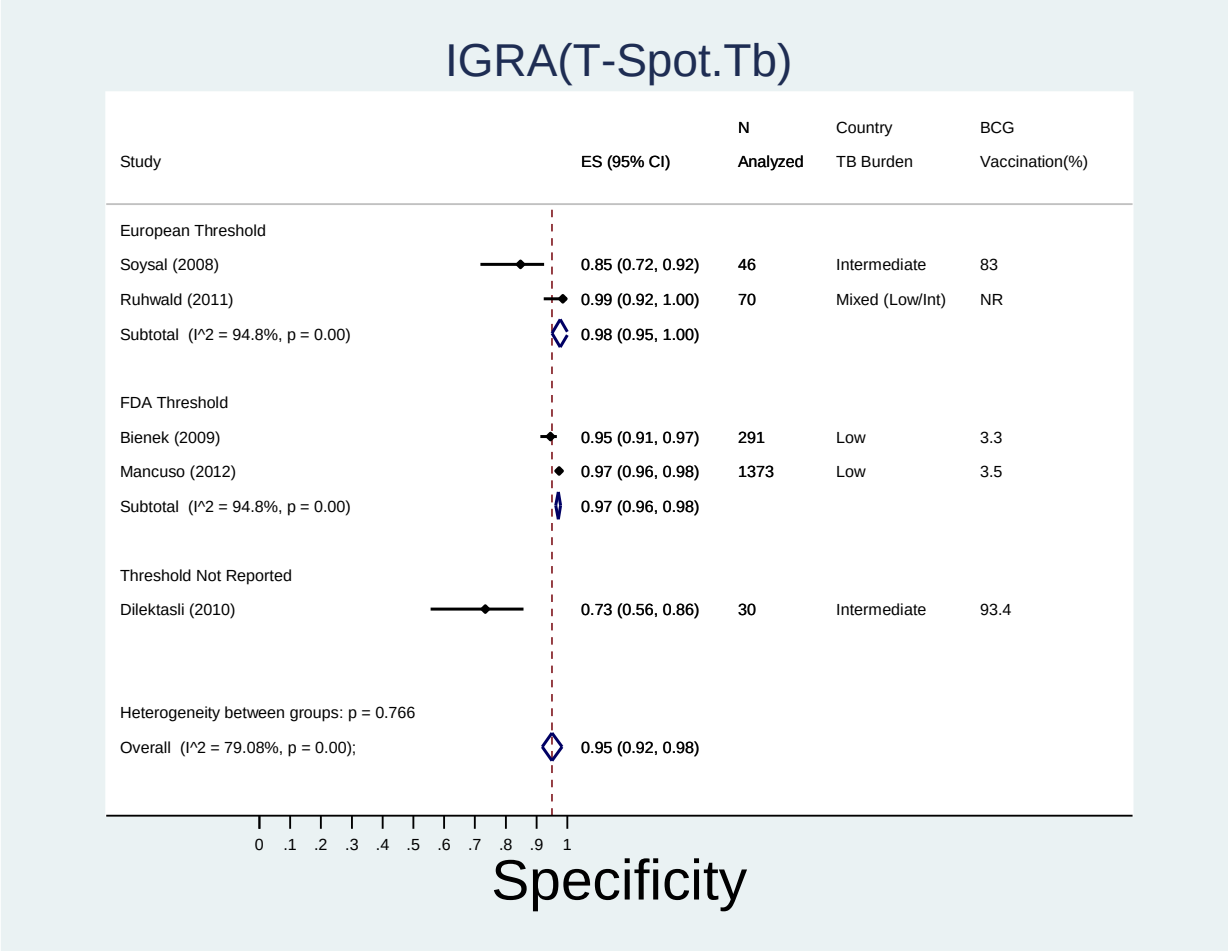
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; N=number; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 37. Specificity of TST at 15-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Population



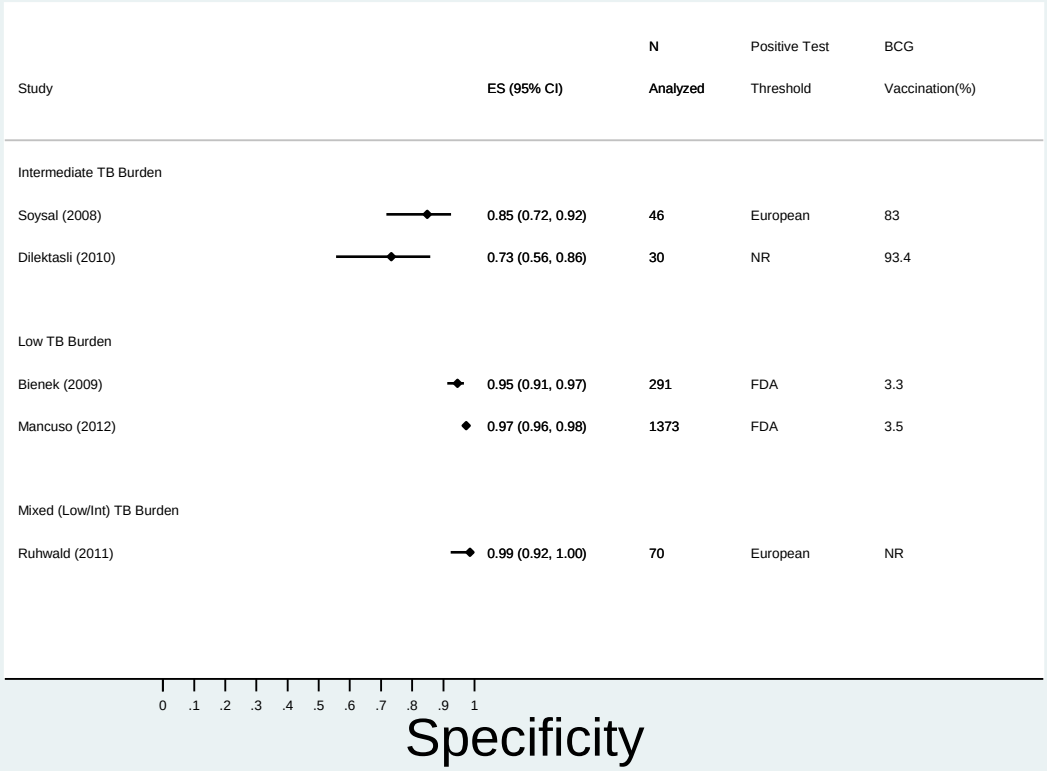
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; N=number; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 38. Specificity of IGRA (T-SPOT.*TB*) Test, Stratified by Threshold Used to Consider Test Positive



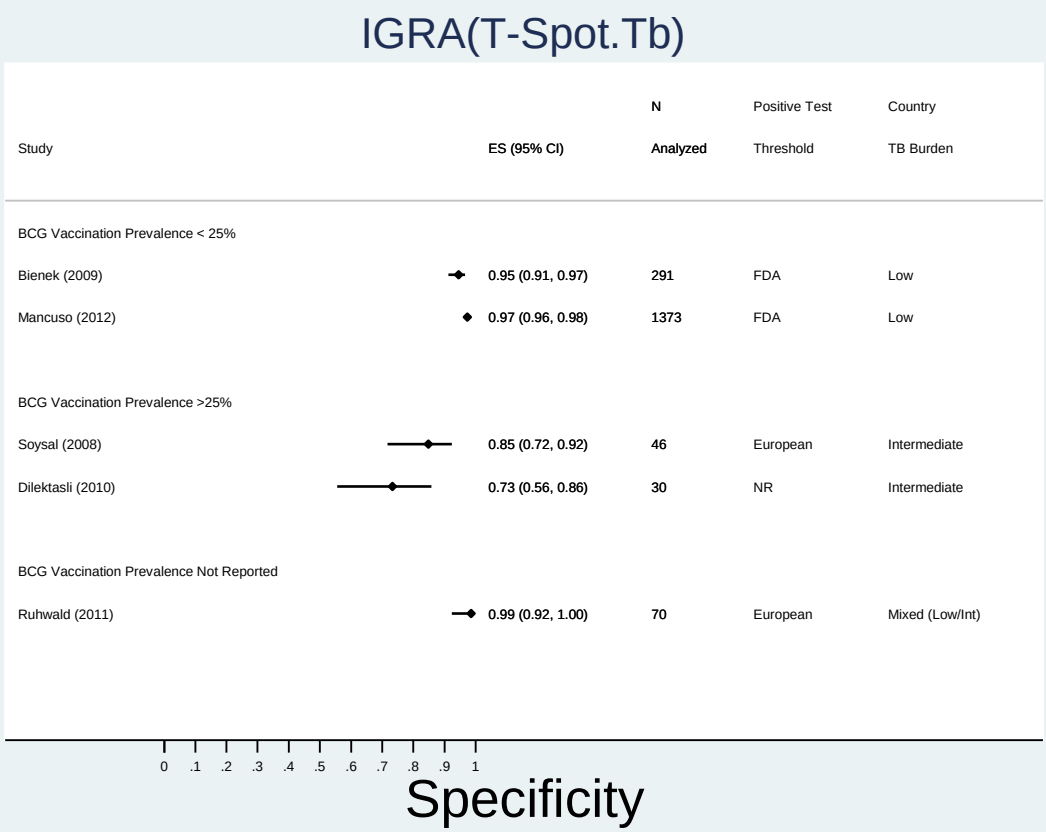
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; FDA=U.S. Food and Drug Administration; IGRA=interferon-gamma release assay; N=number; TB=tuberculosis.

Appendix F Figure 39. Specificity of IGRA (T-SPOT.*TB*) Test, Stratified by Country TB Burden of the Study Setting



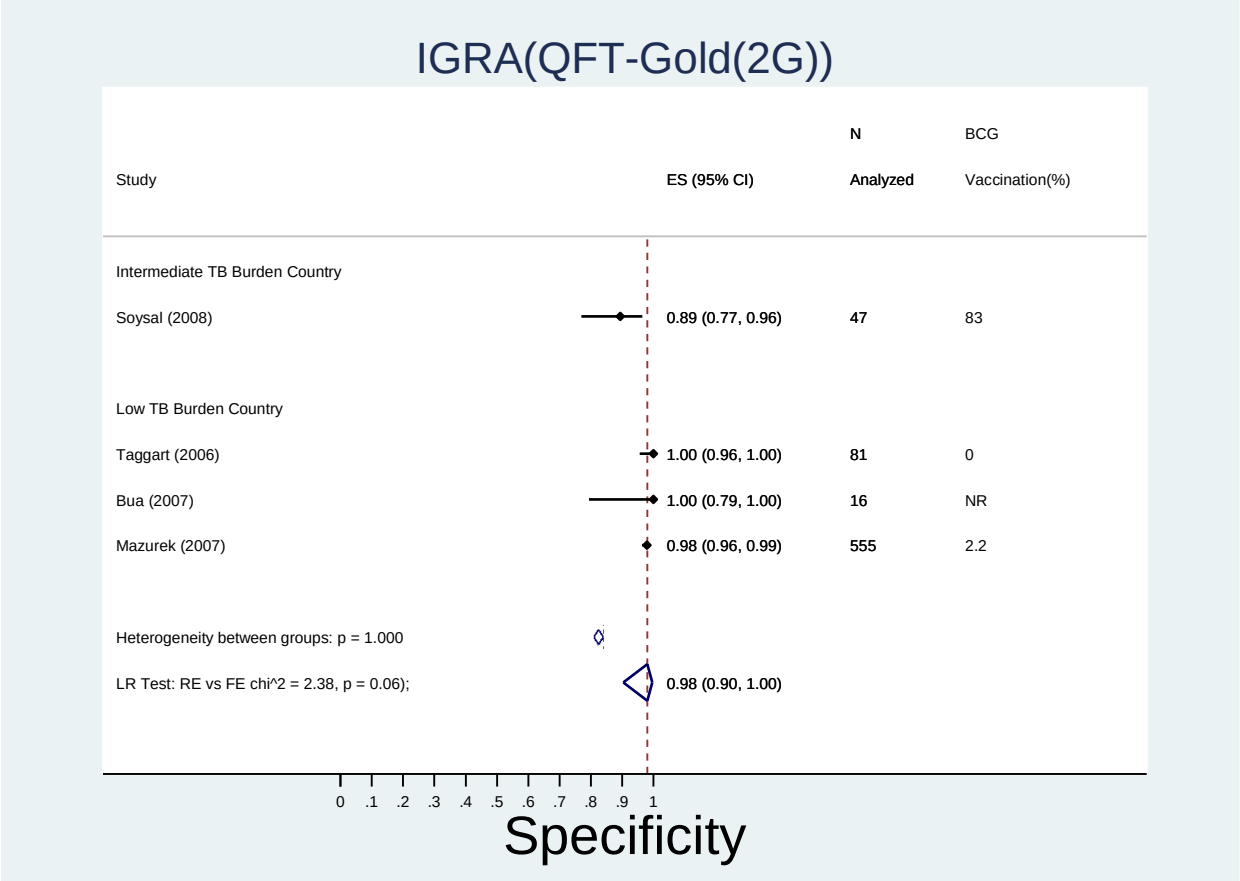
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; IGRA=interferon-gamma release assay; N=number; TB=tuberculosis.

Appendix F Figure 40. Specificity of IGRA (T-SPOT.*TB*) Test, Stratified by BCG Vaccination Prevalence of the Study Population



Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; FDA=U.S. Food and Drug Administration; IGRA=interferon-gamma release assay; N=number; TB=tuberculosis.

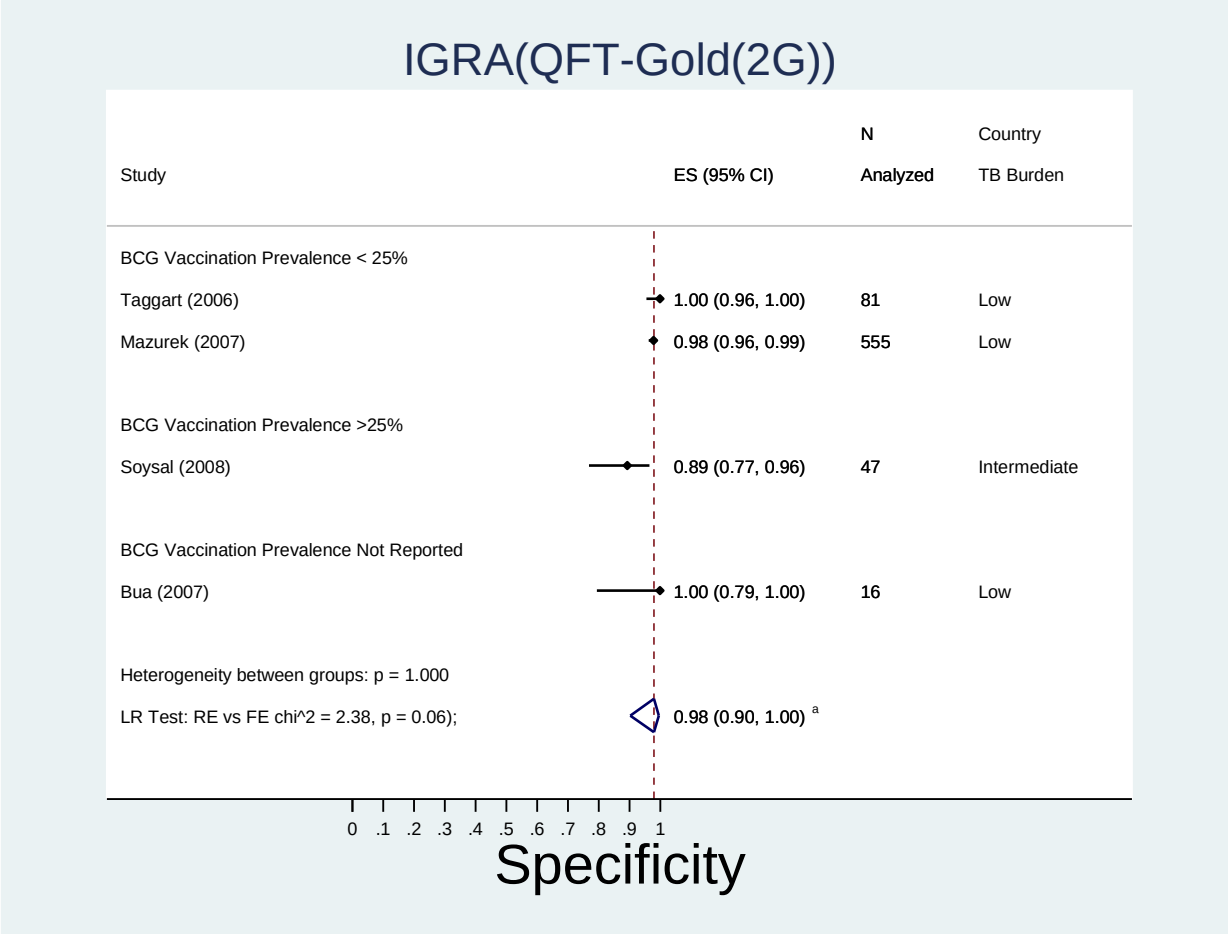
Appendix F Figure 41. Specificity of QFT-Gold (2nd-Generation), Stratified by Country TB Burden of the Study Setting



[a] Subgroup pooled estimate using maximum likelihood estimator because of two point estimates of 1.0.

Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

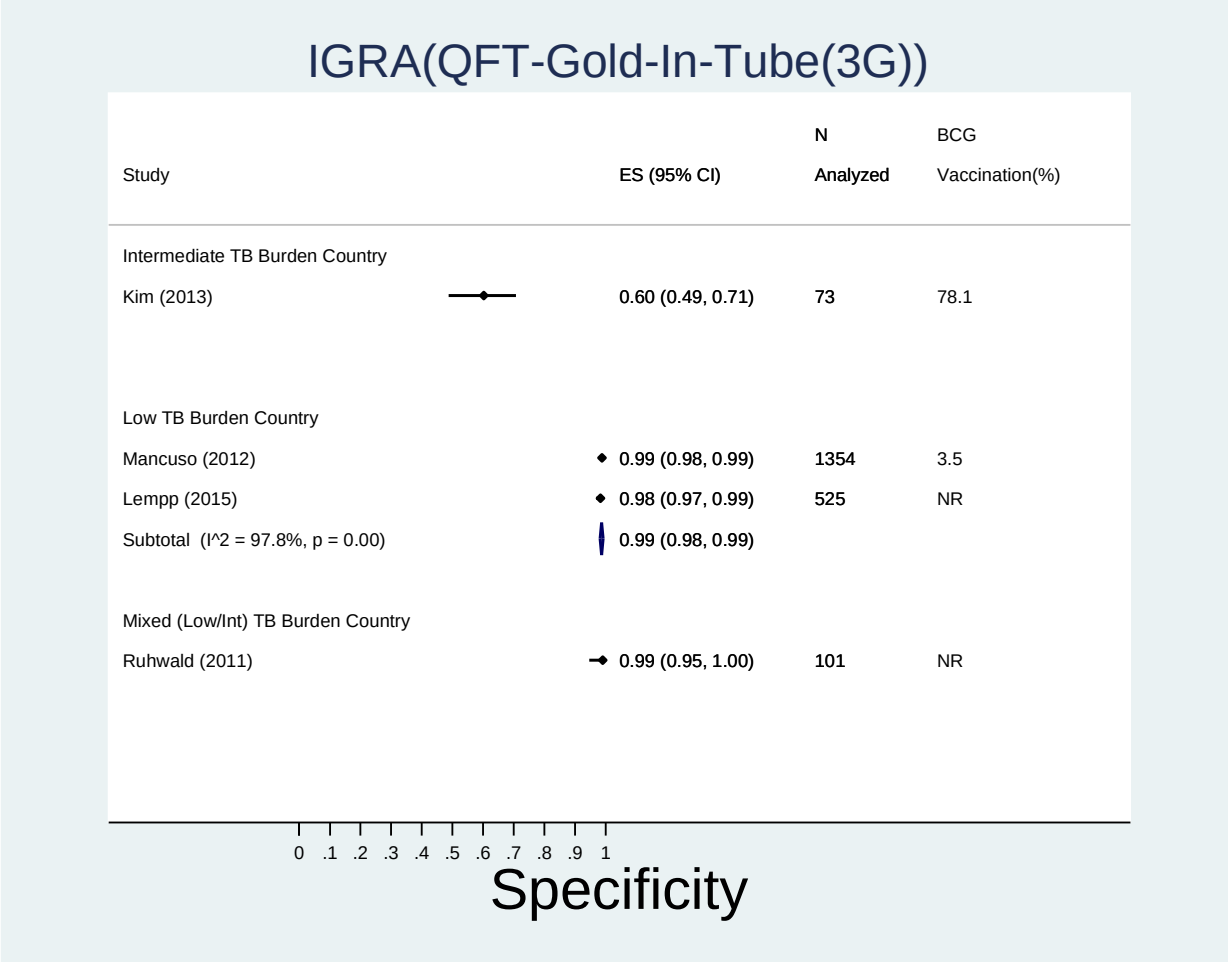
Appendix F Figure 42. Specificity of QFT-Gold (2nd-Generation), Stratified by BCG Vaccination Prevalence of the Study Population



[a] Pooled estimate using maximum likelihood estimator because of two point estimates of 1.0.

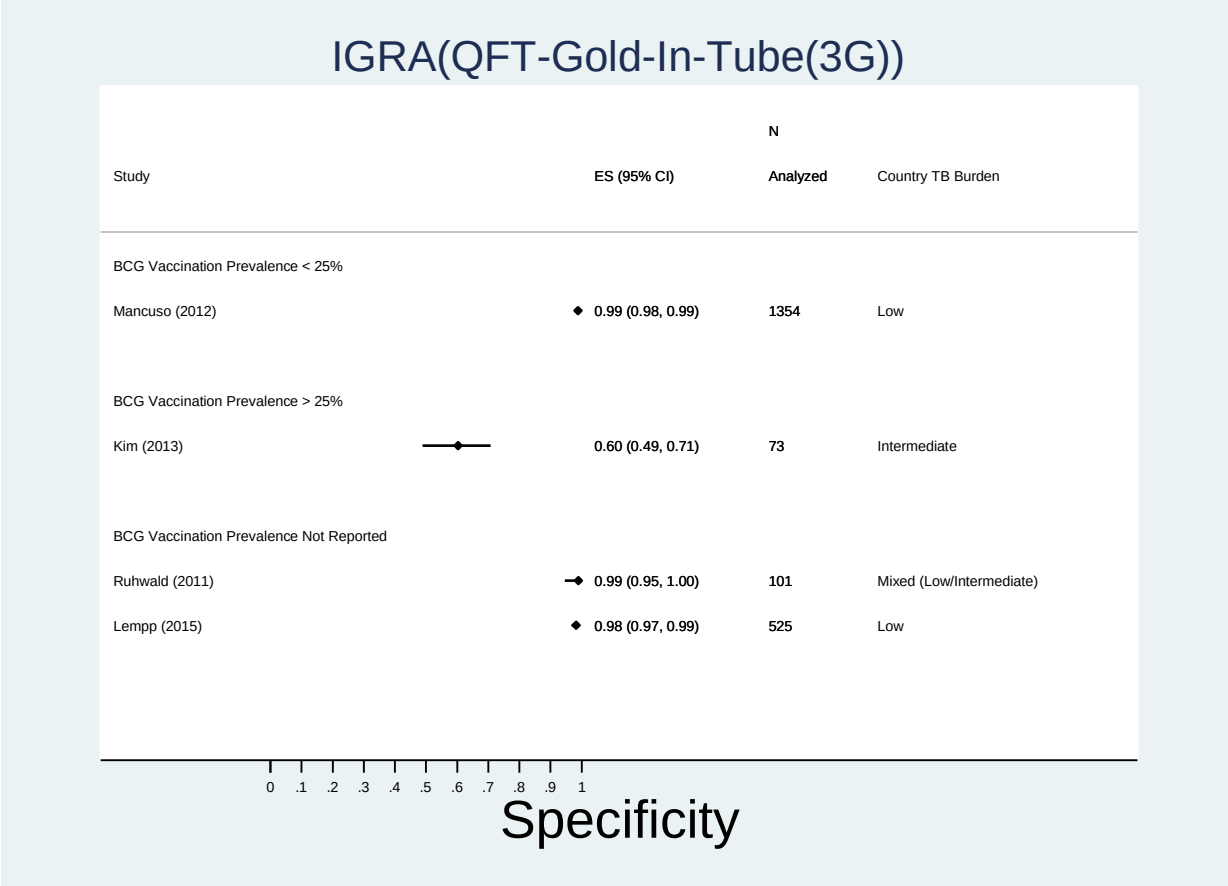
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; IGRA=interferon-gamma release assay; N=number; TB=tuberculosis.

Appendix F Figure 43. Specificity of QFT-Gold In-Tube (3rd-Generation), Stratified by Country TB Burden of the Study Setting



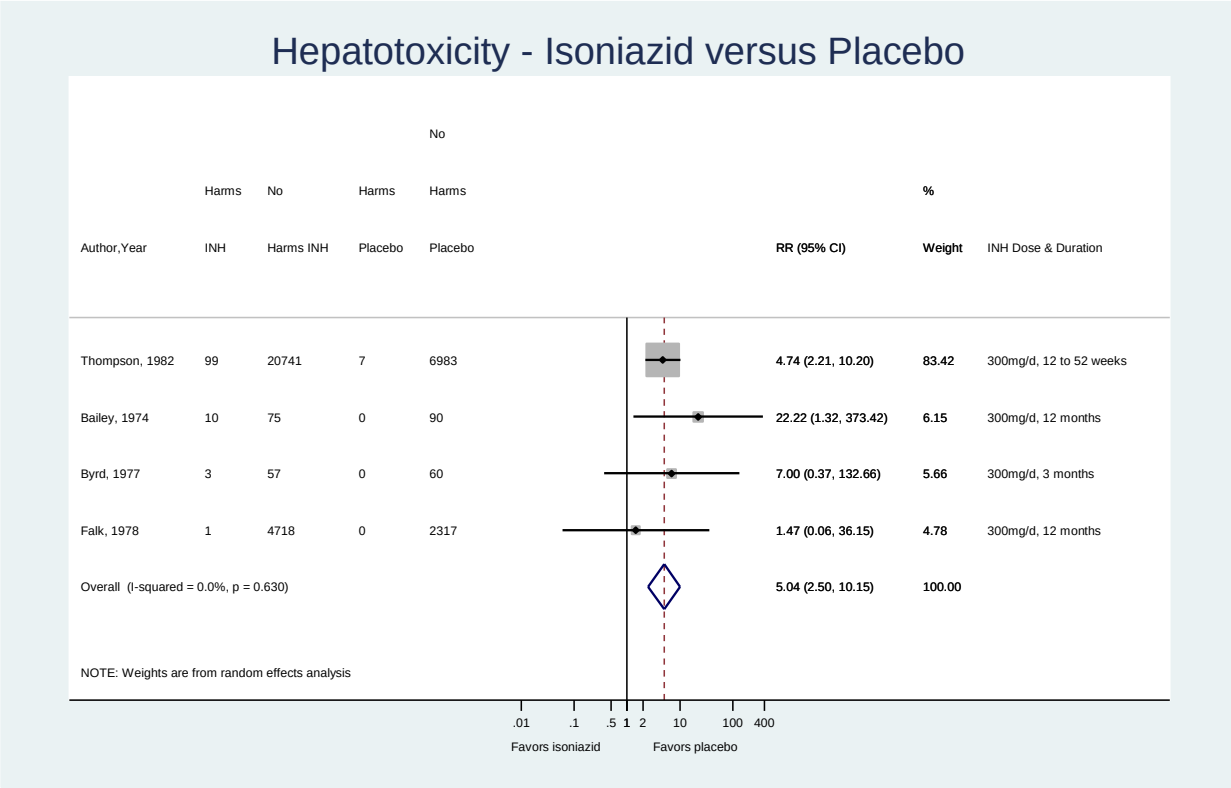
Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; IGRA=interferon-gamma release assay; N=number; NR=not reported; TB=tuberculosis.

Appendix F Figure 44. Specificity of QFT-Gold In-Tube (3rd-Generation), Stratified by BCG Vaccination Prevalence of the Study Population



Abbreviations: BCG=bacille Calmette-Guérin; CI=confidence interval; ES=effect size; IGRA=interferon-gamma release assay; N=number; TB=tuberculosis.

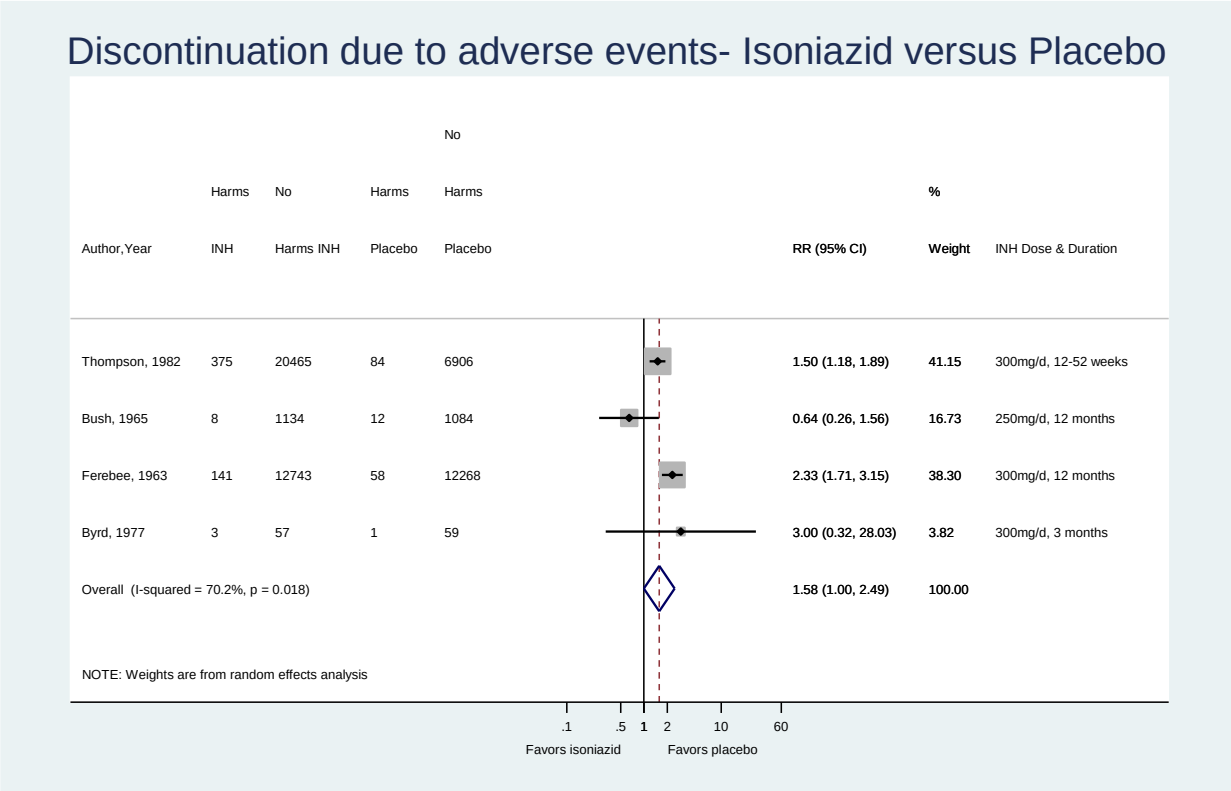
Appendix G Figure 1. Isoniazid Compared With Placebo, Relative Risk of Developing Hepatotoxicity: Sensitivity Analysis Including Data From Four Randomized, Controlled Trials



Notes: For Thompson 1982 (IUAT trial), we included data from the 12-, 24-, and 52-week groups. A definition for hepatotoxicity (presented as "hepatitis" in this study) was not reported for this study. For Bailey 1974 and Byrd 1977, hepatotoxicity was defined as SGOT >100 mU/mL. For Falk 1978, hepatotoxicity was defined only as "mild hepatitis."

Abbreviations: CI=confidence interval; INH=isoniazid; RR=relative risk.

Appendix G Figure 2. Isoniazid Compared With Placebo, Relative Risk of Treatment Discontinuation Due to Adverse Events: Sensitivity Analysis Including Data From Four Randomized, Controlled Trials



Notes: For Thompson 1982 (IUAT trial), rates of discontinuation due to adverse events were reported only as a combined value across the three treatment duration groups (12-, 24-, and 52-week). For Bush 1965, treatment discontinuation due to adverse events was categorized as gastrointestinal, rash, and other. For Byrd 1977, treatment discontinuation was due to "symptomatology," which included hepatotoxicity and mild nausea/abdominal cramps. For Ferebee 1963, discontinuation due to adverse events corresponded to participants stopping medication due to being "sick" from pills.

Abbreviations: CI=confidence interval; INH=isoniazid; RR=relative risk.