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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 the evidence on benefits and harms of screening for and treatment of latent tuberculosis infection (LTBI) for adult populations and settings relevant to primary care in the United States.

Data Sources: PubMed/MEDLINE, the Cochrane Library, and trial registries through December 3, 2021; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through July 22, 2022.

Study Selection: English-language controlled studies evaluating (1) screening for LTBI with the tuberculin skin test (TST) using the Mantoux method or commercial interferon-gamma release assays (IGRAs) or (2) treatment of LTBI with pharmacotherapy regimens that are currently recommended by the Centers for Disease Control and Prevention. 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 excluded studies of persons with underlying immunosuppression and for whom LTBI testing is considered part of standard disease management (e.g., persons with the human immunodeficiency virus, planned or active use of targeted immune modulators).

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: This review included 113 publications (69,009 participants); 101 of those assessed screening test accuracy or reliability. No studies evaluated benefits and harms of screening compared with no screening. Pooled estimates for sensitivity of the TST at the 5-mm and 10-mm induration thresholds for positivity were 0.80 (95% confidence interval [CI], 0.74 to 0.87) and 0.81 (95% CI, 0.76 to 0.87), respectively. The pooled estimate at the 15-mm threshold was 0.60 (95% CI, 0.46 to 0.74). Pooled estimates for sensitivity of IGRA tests ranged from 0.81 (95% CI, 0.79 to 0.84) for the QuantiFERON-TB Gold-In-Tube® test (3rd-generation test) to 0.90 (95% CI, 0.87 to 0.92) for T-SPOT.*TB*. Pooled estimates for specificity of screening tests ranged from 0.95 to 0.99. For treatment of LTBI, a large (N=27,830) good-quality randomized, controlled trial (RCT) found a relative risk (RR) for progression to active TB at 5 years of 0.35 (95% 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., using a longer duration of treatment than currently recommended) found an RR of 0.31 (95% CI, 0.24 to 0.41; 5 RCTs; N=36,823). A previously published meta-analysis reported that multiple regimens were efficacious compared with placebo or no treatment, including isoniazid regimens of 6 months (odds ratio [OR], 0.65 [95% credible interval [CrI], 0.50 to 0.83] vs. placebo) or longer, rifampin plus isoniazid regimens of 3 to 4 months (OR, 0.53 [CrI, 0.36 to 0.78] vs. placebo), and weekly rifapentine plus isoniazid regimens (OR, 0.36 [CrI, 0.18 to 0.73] vs. no treatment). For harms, a large (N=27,830) good-quality RCT reported an RR for hepatotoxicity of 4.59 (95% CI, 2.03 to 10.39; number needed to harm, 279) for 24 weeks of isoniazid compared with placebo. Our sensitivity analyses adding three RCTs that did not meet all of our eligibility criteria (e.g., longer duration of isoniazid) yielded a similar result (pooled RR, 5.04 [95% CI, 2.50 to 10.15]; 4 RCTs; N=35,161). Our meta-analyses found greater risk for

hepatotoxicity with isoniazid than with rifampin (pooled RR, 4.22 [95% CI, 2.21 to 8.06], N=7,339). A previously published network meta-analysis reported greater odds of hepatotoxicity with regimens of longer duration (OR vs. no treatment [95% CrI]: isoniazid 6 months, OR 1.10 [0.40 to 3.17]; isoniazid 9 months, OR 1.70 [0.35 to 8.05]; isoniazid plus rifapentine, 0.52 [0.13 to 2.15], rifampin 3–4 months 0.14 [0.02 to 0.81], isoniazid plus rifampin 3-4 months, 0.72 [0.21 to 2.37]).

Limitations: Tests for the direct diagnosis of LTBI are not available. Thus, studies estimated accuracy using patients with confirmed active TB to establish sensitivity and healthy, low-risk persons to establish specificity. The applicability to other populations is somewhat uncertain. The single placebo-controlled trial meeting all eligibility criteria that established the effectiveness of isoniazid for preventing active TB was published more than 40 years ago and was conducted among subjects with pulmonary fibrotic lesions; it may overestimate the benefits of treatment for populations with lower risk for progression. Contemporary treatment studies have not included placebo arms; benefits and harms of newer treatments were estimated from comparative studies.

Conclusions: No studies evaluated the benefits and harms of screening for LTBI compared with no screening. TST and IGRAs are moderately sensitive and highly specific. Treatment of LTBI with recommended regimens reduces the risk of progression to active TB. Isoniazid is associated with higher rates of hepatotoxicity than placebo or rifampin.

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Chapter 1. Introduction

Scope and Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to inform an update of its recommendation on screening for latent tuberculosis infection (LTBI) in adults. In 2016, the USPSTF recommended screening for LTBI in asymptomatic adults at increased risk (B recommendation).[1] The purpose of this report is to review the current evidence on targeted screening for and treatment of LTBI in populations and settings relevant to primary care in the United States.

This review was scoped to inform an updated recommendation about LTBI screening in asymptomatic adults in settings relevant to primary care. The review does not cover testing of close contacts of persons with active tuberculosis (TB) (usually managed by public health programs) or high-risk populations for whom LTBI testing is considered part of standard disease management (e.g., persons with HIV, head and neck cancer, leukemia or lymphoma, silicosis, a history of or planned organ transplant, planned or active use of tumor necrosis factor-alpha inhibitors or other targeted immune modulators, and planned or active use of chemotherapy).

Condition Definition

Mycobacterium tuberculosis is the bacteria that causes TB. 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 and can be spread to others by airborne transmission. If another person inhales air containing these droplet nuclei, three outcomes are possible: clearance of the bacteria with no resulting infection; onset of active disease (primary TB disease); or LTBI—that is, potential dissemination and containment of the bacteria by the immune system at various sites without apparent signs, symptoms, or radiographic or bacteriologic evidence of TB disease.[2] Persons with LTBI are not infectious to others. LTBI can later progress to active TB disease when previously dormant *M. tuberculosis* bacteria overcome immune containment, proliferate, and progress. Persons with active TB disease have symptoms such as cough (often producing sputum or blood), fevers, chills, weight loss, and night sweats.

Prevalence and Burden of Disease/Illness

TB is a substantial health issue globally with an estimated 1.7 billion infected with LTBI (23% of the world's population) in 2014; there were approximately 10 million cases of active TB with 1.5 million TB-related deaths worldwide in 2020.[3, 4] In the United States, active TB is a more limited health problem with cases declining in recent decades. In 2019, 8,904 new active TB cases were reported in the United States, corresponding to an incidence rate of 2.7 cases per 100,000 population.[5] There were 526 deaths from TB disease in the United States in 2019.[6] In 2020, the incidence rate was down to 2.2 cases per 100,000 (7,174 new active TB cases).[7]

Although factors related to the COVID-19 pandemic may be responsible for some of that decrease from 2019 to 2020, the incidence rate and number of deaths from TB have steadily declined over the past 40 years.

In 2020 in the United States, 5,127 active TB cases occurred among persons born outside the US (71.5% of all cases), for a rate of 11.7 cases per 100,000 population compared with 2,018 cases and a rate of 0.7 cases per 100,000 population among U.S.-born persons.[8] The top five countries of birth among persons born outside the US in the United States with new TB in 2020 were Mexico (18.0%), the Philippines (12.5%), India (10.4%), Vietnam (8.2%), and China (5.1%), accounting for 54.2 percent of total cases.[9] Most of these cases are thought to be due to progression of latent infection (to active TB disease) rather than new transmission within communities.[10-15] Active TB rates also vary by race/ethnicity: about 89 percent of all TB cases occur among racial and ethnic minority groups.[16] Compared with White persons, TB case rates per 100,000 in 2020 were 47 times higher among Native Hawaiians/Pacific Islander persons, 33 times higher for Asian persons, 9 times higher for Hispanic or Latino persons, 8 times higher for American Indians/Alaska Native persons, and 8 times higher for Black/African American persons.[17, 18] In 2020, among the 5,127 persons born outside the US with active TB, 9.7 percent were diagnosed within 1 year after arrival in the United States, 17.8 percent were diagnosed from 1 to 4 years after initial arrival, and 32.3 percent were diagnosed at least 20 years after arrival.[19] The incidence of active TB in the United States also varies by geographic location and living accommodations. Whereas the overall U.S. TB rate for 2020 was 2.2 cases per 100,000, State-specific rates ranged from 0.0 (Wyoming) to 7.9 (Alaska).[20] Although seven States and the District of Columbia reported TB rates higher than the national average (Alaska, California, Hawaii, Maryland, New Jersey, New York, Texas, and Washington, DC), four States accounted for about 50 percent of all U.S. TB cases (California, Texas, New York, and Florida).[20]

Although the World Health Organization (WHO) estimates that one quarter of the world population has LTBI, 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 required to be reported to the Centers for Disease Control and Prevention's (CDC's) National Notifiable Disease Surveillance System.[21, 22] However, LTBI has standardized case definitions; jurisdictions are free to report LTBI cases to CDC if they choose, and latent infection may require reporting to local or State public health authorities.[23] Unlike active TB disease, which is diagnosed on the basis of clinical signs and symptoms and usually confirmed by identification of *M. tuberculosis* from fluid or tissue specimens, tests to help determine if a person has LTBI measure memory T-cell response, an indirect measure of host sensitization to *M. tuberculosis*.[24] In general, estimates of the prevalence of LTBI are based on studies using tuberculin skin test (TST) or interferon-gamma release assay (IGRA) to define infection.

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

the US who are 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.[25] Other than persons born outside the US, 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 persons born outside the US are not available. Other researchers have estimated the prevalence of LTBI in the United States using verified TB cases for 2011 through 2015 from the U.S. National TB Surveillance System, the 2010 U.S. Census results, and previously reported estimates of reactivated TB, to conclude the U.S. prevalence rate for LTBI during those years was 3.1 percent (uncertainty limits 2.2% to 5.2% based on higher or lower reactivation assumptions), corresponding to 8.9 (6.3 to 14.8) million infected persons.[26] Of the 3,143 counties across the United States, prevalence estimates varied widely: estimated prevalence was 0 to 1 percent in 63 percent of counties, 1 to 3 percent in 21 percent of counties, and greater than 3 percent in 12 percent of counties. States with the most clusters of counties with the highest prevalence estimates were located primarily in the U.S. Southeast and Southwest regions, plus Hawaii, Alaska, and the southern half of California.[26]

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 persons experiencing homelessness in New York City over the years 1992 through 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.[27] A review published in May 2015 offered 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 varied by test used (TST or IGRA) and, in some cases, were based on a single study (Appendix A Contextual Question [CQ] 1 provides additional information on the estimates and risk assessment tools).[24]

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 TST.[28, 29] Five to 10 percent of healthy, immunocompetent persons with a positive TST will progress from LTBI to active TB disease 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.[30, 31] 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 recency of exposure, the size of the TST reaction, and the presence or absence of specific medical conditions.[32]

An 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% CI, 1.2 to 4.7) among those who did not take preventive therapy.[33] A report using 2006 through 2008

U.S. data (not reporting whether patients had taken preventive therapy for LTBI) estimated the rate of progression to active TB among persons with LTBI as 0.084 cases per 100 person-years (95% CI, 0.083 to 0.085).[34] Rates of progression to active TB were higher among persons born outside the US (0.098 cases per 100 person-years [95% CI, 0.096 to 0.100]) than among those born in the United States (0.082 cases per 100 person-years [95% CI, 0.080 to 0.083]).

Risk Factors

Risk factors for TB are typically divided into those associated with risk of exposure and initial infection and those associated with progression to active disease. Both of these categories of risk factors are considered important for addressing TB, including through targeted screening, thresholds for a positive screen, and efforts to eliminate TB in the United States. More specifically, the CDC suggests targeted LTBI screening for those at high risk for TB based on temporary or permanent residence in a country with a high TB rate, current or planned immunosuppression, or close contact with someone who has infectious TB.[35] In addition, the CDC has identified different thresholds for a positive TST based on individual risk factors.[35, 36] Although there is considerable overlap in the risk factors for exposure, initial infection, and progression to active TB disease, these risk factors are often described separately. Many studies that address risk are older and may reflect different background infection rates and practice patterns than today.

Risk factors for initial infection generally include exposure, immunosuppression, and socioeconomic and behavioral factors. A recent synthesis of the literature conducted by the American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), and the CDC provided recommendations on diagnostic testing based on many of these risk factors.[37] More specifically, these recommendations detail risk hierarchies for 1) those with increased risk of infection and 2) those with increased risk of progression to TB if infected in order to guide recommendations for diagnostic testing and interpretation of results. In addition, they combine these risk levels to create a tiered LTBI testing strategy. They categorize levels of risk of infection from lowest to highest as follows:[37] (a) no risk factors, (b) residents and employees of high-risk congregate settings (e.g., prisons), (c) immigrants from high-burden countries (>20 cases of active TB per 100,000 persons in the population), (d) persons who work in mycobacteriology laboratories, and (e) household contacts with or recent exposure to an active TB case. The ATS/IDSA/CDC guidelines describe low, intermediate, and high risk levels for developing active TB if infected.[37] Low risk involves having no risk factors. Intermediate risk is defined as having a clinical predisposition because of diabetes, chronic renal failure, or intravenous drug use. High risk is designated for persons age 5 years or younger, with HIV infection, on immunosuppressive therapy, with an abnormal CXR (chest radiograph) consistent with prior TB, or with silicosis.

Rationale for Screening/Screening Strategies

The rationale for screening for LTBI is to identify persons who may benefit from treatment of latent infection to prevent it from progressing to active TB disease, which can result in morbidity

and mortality for the infected person and pose a risk for transmission to others. The prevention of active TB by treating LTBI is a cornerstone of the public health strategy for eliminating TB in the United States.[38] The WHO has also recognized the prevention of active TB as an essential component of worldwide TB elimination efforts.[4]

The diagnosis of LTBI is based on a clinical assessment and is not based on any single test. If screening tests for LTBI are positive, a medical and social history, symptom assessment, physical examination, imaging tests (typically chest radiographs), and sometimes sputum sampling and other laboratory tests are used to exclude active TB disease (screening tests alone cannot differentiate LTBI from TB disease). Available screening tests for LTBI do not directly determine the presence of *M. tuberculosis*, for example, with cultures or nucleic acid assays as is typically done when screening for other infections. Instead, available screening tests assess the immune response following an exposure to *M. tuberculosis* antigens. The TST and IGRA are the two categories of tests widely available for screening for LTBI. Because these tests are indirect markers of infection, they cannot be used to distinguish persons with latent infection, active disease, or convalescing patients. Further, because the diagnosis of LTBI is clinical, no reference diagnostic tests are available for confirming an LTBI diagnosis. Thus, the evaluation of screening test accuracy of TST and IGRA requires case-control study designs, also known as two-gate designs, where the sensitivity of the tests is evaluated among persons with confirmed active TB disease, and the specificity of the tests is evaluated among healthy individuals from low-TB-incidence areas and without known exposure or TB risks (i.e., persons with presumptive absence of LTBI).

TST

The TST, also known as the Mantoux test, has been the standard screening test for LTBI for many years.[37] This test involves the intradermal placement of a standardized tuberculin antigen (e.g., 5 units of purified protein derivative [PPD-S2] in the United States, 2 units of PPD-RT-23 in other regions of the world), typically on the ventral surface of the forearm followed by clinical measurement of the delayed hypersensitivity reaction, if any, by a trained observer 48 to 72 hours after placement.[37, 39] The observer measures the transverse diameter of any palpable induration and records its size in millimeters. Indurations of 5 mm or more are considered positive for close contacts of active TB cases; immunosuppressed individuals, including those with HIV; persons receiving tumor necrosis factor blocking agents; and persons with clinical or radiographic evidence of current or prior TB. An induration of 10 mm or more is considered a positive test for persons born in countries with high TB incidence, those with occupational exposure to TB, and those with medical conditions that increase the risk of progression from LTBI to active TB disease (e.g., diabetes, chronic renal failure). For all other persons, an induration of 15 mm or more is considered a positive test. Benefits of the TST include its low cost, no requirement for blood draw or laboratory or complex equipment, and years of established use with standardized definitions for positive tests.[37] However, TST requires trained personnel to administer and interpret the test, requires two visits, and may result in false-positive results because of cross-reactivity with the Bacille Calmett-Guérin (BCG) vaccine and nontuberculous mycobacteria and may result in false-negative results in children and in individuals with immunosuppression.[39]

IGRAs

IGRAs are in vitro laboratory tests that can also be used for screening for LTBI. These tests measure the CD4 T-cell response specific to *M. tuberculosis* antigens and do not react in response to most nontuberculous strains of mycobacteria, including the *M. bovis* strains associated with the BCG vaccine (although actual *M. bovis* infection can cause a positive IGRA). Two commercial platforms for conducting IGRAs are Food and Drug Administration (FDA) approved: QuantiFERON-TB® (QFT) and T-SPOT®.*TB*. QFT offers two whole-blood enzyme-linked immunosorbent assays: the QFT-Gold in tube (QFT-GIT, approved in 2007) and the QFT-Gold Plus (approved in 2017). The T-SPOT.*TB* test (approved in 2010) is an enzyme-linked immunospot assay that is conducted on separated monocytes and lymphocytes. In clinical practice, the results of the QFT and T-SPOT.*TB* tests are interpreted qualitatively as positive or negative based on whether the quantitative result is above or below a specific threshold; however, results may also be reported as borderline (T-SPOT.*TB* only) or indeterminate.[37] Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors. Benefits of IGRAs include increased specificity for *M. tuberculosis* and lack of need for a return visit for interpretation. However, IGRAs are more costly than TST; require a blood draw; and require proper and timely specimen collection, storage, and processing.

Treatment Approaches

Individuals who screen positive for LTBI and in whom active infection has been excluded are generally offered treatment with antimycobacterial medications based on trials that demonstrate reduced progression to active TB by treating latent infections.[36] For decades, isoniazid (INH) was the only medication used for treating LTBI, based on trials demonstrating its effectiveness for preventing progression to active TB and its low cost. However, concerns about hepatoxicity and low treatment completion rates for regimens as long as 6 to 12 months prompted the evaluation of alternative regimens. Since then, several preferred regimens have emerged that include INH and drugs in the rifamycin class (rifampin [RIF] and rifapentine [RPT]). In 2020, the CDC issued new recommendations (**Table 1**) based on findings from a systematic review and meta-analysis of newer clinical trials of rifamycin-based regimens to treat LTBI, which demonstrated equivalent efficacy and superior safety and completion rates for shorter rifamycin-based regimens compared with the standard comparator regimen of daily INH for 9 months.[40] The three rifamycin-based regimens (once-weekly INH plus RPT for 3 months, daily RIF for 4 months, and daily INH plus RIF for 3 months) were designated as preferred because they have excellent tolerability and efficacy, shorter treatment duration, and higher completion rates. Daily INH for 6 months was designated as an alternative regimen because of its excellent efficacy but longer treatment duration and lower completion rates (and therefore lower real-world effectiveness). Daily INH for 9 months was designated as a conditional alternative regimen because of the potential for increased risk of hepatotoxicity with its longer duration and unclear increase in effectiveness. The CDC notes that intermittent regimens (once weekly) should be provided by directly observed therapy (DOT).

Clinical Practice in the United States and Recommendations of Other Organizations

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 (**Appendix A Table 1**).[37] Recommendations for targeted—rather than routine—LTBI screening for specific high-risk populations have mostly remained unchanged in recent years. The CDC recommends that those at increased risk for LTBI and TB disease should be tested for LTBI.[37, 41] The CDC provides a three-item example TB risk assessment tool to help identify those who should be tested, based on a tool from the California Department of Public Health.[35] The tool includes three of the major risk factor categories: temporary or permanent residence of 1 month or greater in a country with a high TB rate, current or planned immunosuppression, and close contact during lifetime with someone who has had infectious TB disease. CQ 1 in Appendix A provides additional information about risk assessment tools.

In 2017, the CDC, in collaboration with the ATS and IDSA, revised joint recommendations for LTBI screening, which are largely consistent with prior recommendations.[37] TST remained the preferred method of LTBI testing for children under the age of 5 years. In individuals older than 5 years, an IGRA was recommended over TST for patients likely to be infected with *M. tuberculosis* and who have *low or intermediate* risks for disease progression, especially among those with prior BCG vaccinations or who might not return to have TSTs read (e.g., persons experiencing homelessness). In individuals older than 5 years who are likely to be infected with *M. tuberculosis* with a *high* risk for disease progression, TST or an IGRA can be used without preference. Of note, the Red Book from the American Academy of Pediatrics indicates that an IGRA can be used for children 2 years or older.[42]

The CDC discourages the use of TST and IGRA tests for LTBI among individuals and populations at low risk for TB infection and discourages a testing approach that is independent of a risk assessment.[37] Although the recommendation is not to test individuals at low risk for *M. tuberculosis* infection, in cases where LTBI testing is otherwise required (e.g., by law), use of an IGRA is preferred over TST. For all scenarios among individuals older than 5 years, if an IGRA is not available, is cost prohibitive, or is too burdensome, TST remains a reasonable alternative. For testing done among individuals at low risk (e.g., when required by law), a second confirmatory test is recommended for individuals older than 5 years for whom the first test is positive; in such cases, latent infection is confirmed only if both tests are positive and active TB disease is ruled out.[37] The second test may be either an IGRA or TST.[37]

Many of the WHO guidelines are largely targeted toward TB control programs and public health authorities in low- and middle-income countries.[43, 44] In 2018, the WHO reaffirmed their recommendation for asymptomatic individuals of all ages in countries with a low TB incidence who are household contacts of persons with active TB to be systematically tested and treated for LTBI.[45] The WHO endorses the use of TST or IGRAs as LTBI screening methods.[45] The WHO also states that systematic testing for and treatment of LTBI may be considered in countries with a low TB incidence for persons residing in correctional facilities, health workers, immigrants

from countries with a high TB burden, persons experiencing homelessness, and persons who use illicit drugs.[45]

Chapter 2. Methods

Key Questions and Analytic Framework

The scope and key questions (KQs) were developed by the Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers. The analytic framework and KQs that guided the review are shown in **Figure 1**. Five KQs were developed for this review:

1. What are the benefits of targeted screening for LTBI in primary care settings in asymptomatic adults who are at increased risk for developing active tuberculosis (TB), including among specific populations of interest?

2a. What are the accuracy and reliability of the tuberculin skin test (TST) or interferon-gamma release assay (IGRA) for screening in asymptomatic adults who are at increased risk for developing active TB disease, including among specific populations of interest?

2b. What are the accuracy and reliability of sequential screening strategies that use TST and IGRA in asymptomatic adults who are at increased risk for developing active TB disease, including among specific populations of interest?

3. What are the benefits of treatment for LTBI with Centers for Disease Control and Prevention (CDC)-recommended pharmacotherapy regimens, including among specific populations of interest?

4a. Are harms associated with screening for LTBI, including among specific populations of interest?

4b. Do these harms differ by screening method or strategy?

4c. Do these harms differ by population?

5. What are the harms associated with treatment of LTBI with CDC-recommended pharmacotherapy regimens, including among specific populations of interest?

For all KQs, this review looked for evidence on whether results differ for specific populations of interest, including those defined by age, sex, race/ethnicity, pregnancy, and higher risk for developing TB. In addition to addressing the KQs, this review looked for evidence related to one CQ that focused on risk assessment tools available for use in primary care to identify adults to screen for LTBI. The CQ was not part of this systematic review. CQs are intended to provide additional background information. Literature addressing the CQ is summarized in **Appendix A**.

Data Sources and Searches

We searched PubMed/MEDLINE and the Cochrane Library for English-language articles published from January 30, 2015, through December 3, 2021. 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 B**. Targeted searches for unpublished literature were conducted by searching ClinicalTrials.gov. To supplement electronic searches, the reference lists of pertinent review articles and studies that met the inclusion criteria were reviewed. Studies

suggested by peer reviewers or public comment respondents were also reviewed and, if appropriate, incorporated into the final review. Since December 3, 2021, ongoing surveillance was conducted through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on July 22, 2022. All literature search results were managed using EndNote™ version 9.2 (Thomson Reuters, New York, NY).

Study Selection

We selected studies based on inclusion and exclusion criteria for populations, interventions, comparators, outcomes, timing, settings, and study designs that we developed with input from the USPSTF (**Appendix B**). In addition to studies identified in the update searches, we reassessed all studies included in the previous review for the USPSTF against the updated study selection criteria. We included relevant English-language studies of good or fair quality and 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, randomized, controlled trials (RCTs) or prospective cohort studies were eligible if they compared screening with no screening and focused on asymptomatic adults belonging to populations at increased risk for developing active TB (e.g., persons who inject drugs, persons experiencing homelessness or residing in homeless shelters, persons residing in correctional facilities, 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 (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, we relied on data from studies of persons with bacteriologic-confirmed, active TB who had not yet received treatment (or who had received no more than a few weeks of treatment) to determine sensitivity and 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 commercially available IGRAs (T-SPOT.*TB*, QFT-GIT, and QFT-Gold Plus) using the manufacturers' specified thresholds, 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 and use of standard thresholds for a positive test (i.e., 5 mm, 10 mm, or 15 mm).

For KQs 3 and 5, we included systematic reviews, meta-analyses, and 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 settings considered to be applicable to primary care and conducted in countries categorized as "very high" or "high" on the Human Development Index (as defined by the United Nations Human Development Programme).[46] Study settings considered applicable to primary care included homeless shelters, correctional facilities, college health settings, long-term care facilities, and public health clinics. For KQ 2 sensitivity outcomes (that enrolled persons with active TB disease), we did not set any exclusion criteria based on setting or country; for KQ 2 specificity outcomes (that enrolled persons at low risk for TB), we excluded studies conducted in countries with a high or intermediate TB burden as defined by the WHO (**Appendix B2**).[47]

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 texts to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

We assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B**). Two independent investigators assigned quality ratings for each study. Disagreements were resolved by discussion. Only studies rated as having good or fair quality were included.

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. All data extractions were checked by a second investigator for completeness and accuracy.

Data Synthesis and Analysis

We summarized findings for each KQ in tabular and narrative format. We assessed the overall strength of the evidence for each KQ as high, moderate, low, or insufficient based on the overall quality of the studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence, using methods developed for the USPSTF (and the EPC program).[48] Additionally, the applicability of the findings to U.S. primary care populations and settings was assessed. We resolved discrepancies in strength of evidence grades through consensus discussion.

To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies according to established guidance.[49] The populations, tests, treatments, comparators, outcomes, and study designs were assessed

qualitatively, looking for similarities and differences. When at least three similar studies were available, we conducted quantitative syntheses using random-effects models with the inverse-variance weighted method of DerSimonian and Laird to generate pooled estimates.[50, 51] For KQ 2, we generated separate pooled estimates of sensitivity and specificity because these accuracy data were collected from independent samples. We also generated pooled estimates of sensitivity and specificity stratified by potentially important covariates such as country TB burden, prevalence of BCG vaccination in the study population, timing of testing with respect to the initiation of pharmacotherapy (for sensitivity only), and prevalence of persons with HIV infection. For KQ 2, we assessed statistical heterogeneity through visual inspection of the forest plots because the I^2 statistic has limitations when used for evaluating heterogeneity in diagnostic accuracy studies.[52, 53] For KQs 3 and 5, statistical heterogeneity was assessed using the I^2 statistic when pooled estimates were available. Results for benefits and harms of treatment (KQs 3 and 5) were considered statistically significant if the P value was less than 0.05 based on two-sided testing. All quantitative analyses were conducted using Stata™ version 17 (StataCorp, College Station, TX).

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF website for public comment from March 11, 2021, to April 7, 2021. In response to comments, the USPSTF revised the KQs to clarify intentions and expanded the eligibility criteria to include countries categorized as both "high" and "very high" on the Human Development Index. The final version of the research plan was posted on the USPSTF website on June 17, 2021. The draft evidence review was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments received, mainly to clarify some information in the background. The draft evidence review will also be posted for public comment. Revisions will be made based on comments received, and any references suggested by expert or public reviewers will be evaluated for inclusion/exclusion.

USPSTF and AHRQ Involvement

AHRQ staff and members of the USPSTF participated in developing the scope of work (including the analytic framework and KQs) and reviewed draft reports, but the authors are solely responsible for the content. AHRQ staff provided oversight for the project and assisted in an external review of the draft evidence synthesis.

Chapter 3. Results

Literature Search

We identified 3,801 unique records and assessed 526 full-text articles for eligibility (**Figure 2**). We excluded 413 articles for various reasons, detailed in **Appendix C**, and included 113 articles representing 112 studies. Details of quality assessments of included studies are in **Appendix D Tables 1** and **2**. For most KQs, this review did not find evidence on whether results differ for specific populations of interest (e.g., no subgroup analyses describing effect modification by age or sex). Studies were usually not designed or powered to assess whether results differed for specific populations; any exceptions are described within each KQ below.

Results by Key Question

KQ 1. What Are the Benefits of Targeted Screening for LTBI in Primary Care Settings in Asymptomatic Adults Who Are at Increased Risk for Developing Active TB, Including Among Specific Populations of Interest?

We found no eligible studies that addressed this question.

KQ 2a. What Are the Accuracy and Reliability of the TST or IGRA for Screening in Asymptomatic Adults Who Are at Increased Risk for Developing Active TB Disease, Including Among Specific Populations of Interest?

We identified 101 studies of good or fair quality assessing the sensitivity, specificity, or reliability of one or more of the included screening tests. Thirty-two studies reported on TST and are detailed in **Appendix D Tables 1 and 3**.[54-85] Thirty-nine studies reported on T-SPOT.*TB*.[55, 73-75, 79, 82, 84, 86-117] Twelve studies[106, 107, 116-124125126] reported on QFT-Gold Plus and 51 studies reported on QFT-GIT.[54, 55, 59, 61, 67, 72, 77-80, 86, 90, 94, 99, 101, 103, 104, 106, 107, 115, 116, 118-123, 125, 127-149] Detailed study characteristics for the IGRA tests are reported in **Appendix D Tables 2 and 4**. Across this body of evidence, the mean age of enrolled persons ranged from 30 years to 71 years and the proportion of men ranged from 38 percent to 86 percent. Nineteen studies were conducted exclusively or partly in the United States.[55-57, 60, 63, 65, 66, 68-70, 73, 81, 95, 118, 123, 141, 150-152] We rated 25 studies as good quality and 76 studies as fair quality; individual study quality ratings are in **Appendix E Table 1**.

Sensitivity of Screening Tests

TST

Twenty-one studies estimated sensitivity for TST using various thresholds for a positive test.[54, 56, 58, 59, 62, 64, 67, 70, 72, 74-85] Characteristics of studies are provided in **Appendix D Table 1**. Twelve studies reported sensitivity using a 5-mm induration threshold,[54, 56, 62, 64, 67, 74, 75, 77, 79, 81-83] 15 studies reported sensitivity using a 10-mm induration threshold,[54, 56, 58, 59, 62, 70, 72, 74-78, 81, 84, 85] and nine studies reported sensitivity using a 15-mm induration threshold.[54, 56, 58, 62, 74, 75, 77, 78, 80] Six studies estimating TST sensitivity were conducted in countries with a high TB burden;[54, 59, 78, 80, 82, 83] eight were conducted in countries with an intermediate TB burden;[58, 72, 74-77, 84, 85] and seven were conducted in countries with a low TB burden,[56, 62, 64, 67, 70, 79, 81] including three in the United States.[56, 70, 81]

Five studies included persons who had either not started TB treatment or had started only in the 7 days prior to TST testing,[56, 64, 67, 74, 79] while three studies included those tested between 8 and 14 days after starting treatment[78, 80, 81] and two studies included those tested between 15 and 30 days after starting treatment.[75, 83] Five studies did not report the timing of testing with respect to starting treatment for TB disease.[54, 58, 62, 77, 82]

Three studies[59, 78, 80] provided stratified results for the HIV-negative segment of their population, and 10 studies excluded subjects with HIV from the study.[58, 62, 64, 67, 72, 74, 76, 77, 83, 85] The prevalence of HIV among the four studies that allowed persons living with HIV to enroll ranged from 0.1 percent to 10.8 percent.[56, 79, 81, 153] Four studies did not report the HIV prevalence among the enrolled population.[70, 75, 82, 84] In the 15 studies that reported the BCG vaccination status of enrolled participants, the prevalence of BCG vaccination ranged from 12.4 percent to 100 percent.[54, 56, 58, 59, 62, 67, 74-80, 84, 85]

We calculated pooled estimates for sensitivity of TST by induration threshold (**Table 2, Figure 3**). The pooled sensitivity of TST was 0.80 (95% CI, 0.74 to 0.87; 12 studies; 1,323 participants) with a 5-mm induration threshold, 0.81 (95% CI, 0.76 to 0.87; 15 studies; 1,427 participants) with a 10-mm induration threshold, and 0.60 (95% CI, 0.46 to 0.74; 9 studies; 1,004 participants) with a 15-mm induration threshold. These pooled sensitivities were very similar to those found in the prior report, with the exception of an increase in sensitivity for the 15-mm threshold (0.52 in the prior report). Because of substantial heterogeneity, we stratified TST sensitivity results based on factors that could plausibly alter the sensitivity of TST (**Appendix F Figures 1–12**). These factors included having a higher proportion of persons living with HIV among test subjects and the inclusion of subjects who had already been receiving TB treatment for more than 1 or 2 weeks. We also stratified findings by country burden of TB and prevalence of BCG vaccination among test subjects, which overlap somewhat because persons living in high-TB-burden countries are more likely to have had BCG vaccination, though several studies were conducted in countries with lower TB burden where study subjects had immigrated from higher-burden countries and thus had higher rates of BCG vaccination. We were unable to identify factors that explain heterogeneity in the TST sensitivity estimates, because the stratified analyses for 5-mm threshold studies and some for the 10-mm threshold studies showed no difference among strata, and the analyses for the 15-mm threshold and some for the 10-mm threshold did

not have enough studies in all the strata to meaningfully evaluate findings. Pooled estimates from these stratified analyses showed no meaningful differences from the prior report.

T-SPOT.TB

Thirty-seven studies estimated the sensitivity for T-SPOT.*TB*.[74, 75, 79, 82, 84, 86-117] Characteristics of studies are described in **Appendix D Table 2**. Thresholds for positive test results varied by study: 19 studies used the threshold approved in European Medicines Agency labeling,[74, 75, 82, 84, 87-92, 94, 97-99, 103, 105, 108, 111, 114] 10 studies employed the threshold approved in FDA labeling,[86, 93, 95, 96, 104, 106, 107, 109, 115, 116] and eight studies did not report which threshold was used.[79, 100-102, 110, 112, 113, 117] With regard to baseline TB prevalence within study settings, 12 studies included participants from countries with high TB burden,[82, 100-102, 105, 108-112, 114, 117] while 16 studies were conducted in countries with an intermediate TB burden.[74, 75, 84, 86, 90, 91, 93, 96-99, 103, 106, 107, 113, 116] Seven studies included participants from countries with low TB burden,[79, 87-89, 92, 104, 115] and two studies were conducted in multiple countries that were a mix of low and intermediate TB burden.[94, 95] Only one study was conducted in the United States.[95] Most studies provided information on the timing of tests relative to the initiation of TB treatment among study participants: 16 studies tested prior to or no more than within 7 days of starting TB treatment,[74, 79, 82, 84, 88, 95, 97, 98, 101, 103, 104, 109-112, 115] six studies tested between 8 and 14 days of initiating TB treatment,[89, 90, 94, 106, 107, 116] and two studies tested within 15 to 30 days of treatment initiation.[75, 108] 13 studies did not provide any data regarding timing of testing with respect to TB treatment initiation.[86, 87, 91-93, 96, 99, 100, 102, 105, 113, 114, 117] HIV prevalence in the enrolled study population was reported in 30 of 37 studies. Among the 14 studies that allowed enrollment of persons living with HIV, the prevalence of HIV ranged from 1.2 percent to 8 percent.[79, 86, 92-96, 103, 104, 106, 111, 113, 115, 117] Sixteen studies reported no enrolled persons with HIV,[74, 88-91, 98-100, 105, 107-110, 112, 114, 116] and the prevalence of HIV was not reported in the remainder of studies. Of the 14 studies reporting the prevalence of BCG vaccination within study populations, the prevalence ranged from 58 to 100 percent.[74, 75, 79, 84, 88, 95, 97, 98, 100, 101, 104, 109, 111, 115]

The pooled sensitivity for T-SPOT.*TB* was 0.90 (95% CI, 0.87 to 0.92; 37 studies; 5,367 participants; I^2=93.2%), **Table 2, Figure 4**). Although there was slightly lower sensitivity reported for studies using the FDA threshold for a positive test (0.86 [95% CI, 0.81 to 0.92]; I^2=87.4%) as compared with the European threshold (0.92 [95% CI, 0.89 to 0.95]; I^2=86.7%), we found no statistically significant or likely clinically meaningful differences in estimates based on test thresholds (**Appendix F Figure 13**). Because we found substantial heterogeneity overall, we conducted stratified analyses based on factors that could plausibly alter the sensitivity (**Appendix F Figures 14–17**). Compared with the last report, sensitivity estimates for countries with low TB burden were lower (0.89 compared with 0.98 in the prior report), but we observed no meaningful differences in sensitivity among low-, intermediate-, or high-TB-burden strata. We found no meaningful differences in sensitivity estimates when stratified by HIV prevalence, BCG vaccination prevalence, or timing of testing with respect to treatment, but these analyses were limited by few studies in some strata and a large number of studies not reporting these characteristics of interest. T-SPOT.*TB* tests returning borderline results ranged from 0 percent[74, 82, 84, 87, 90, 96, 99-102, 105, 106, 109, 110, 112-114] to 6.7 percent[91] among those studies that explicitly reported borderline results. The rest of the studies either did not have any persons with borderline results or excluded such persons from the analysis.

QFT-GIT

QFT-GIT sensitivity was reported in 48 studies.[59, 61, 67, 72, 77-80, 86, 90, 94, 99, 101, 103, 104, 106, 107, 115, 116, 118-122, 125, 127-140, 142-149, 154] Characteristics of studies are described in **Appendix D Table 2**. Thirteen studies were conducted among persons in countries with high TB burden,[59, 78, 80, 101, 127, 131, 134, 136, 137, 142, 146, 148, 154] 25 studies reported on persons from countries with an intermediate TB burden,[61, 72, 77, 86, 90, 99, 103, 106, 107, 116, 120-122, 125, 128-130, 132, 133, 135, 138, 140, 144, 147, 149] and seven studies reported on persons from countries with low TB burden.[67, 79, 104, 115, 119, 143, 145] Three studies were conducted among persons that included a mix of low- and intermediate-TB-burden countries,[94, 118, 139] including one study that reported data from the United States.[118] Twenty-four studies administered tests to participants prior to or no more than within 7 days of initiating TB treatment,[59, 61, 67, 77, 79, 101, 103, 104, 115, 121, 125, 127, 130, 131, 134-136, 140, 142, 144, 145, 147-149] 10 studies tested no more than between 8 and 14 days of treatment initiation,[86, 87, 91-93, 96, 99, 100, 102, 105, 113, 114, 116] and 14 studies did not report any data regarding timing of testing with respect to TB treatment.[72, 86, 99, 119, 120, 128, 129, 132, 133, 137-139, 146, 154] HIV prevalence was reported in 37 studies. Among the 12 studies that allowed enrollment of persons living with HIV, the prevalence of HIV ranged from 1 percent to 15.4 percent.[79, 86, 94, 103, 104, 106, 115, 118, 135, 137, 140, 142] Twenty-four studies did not enroll any persons living with HIV;[59, 61, 67, 72, 77, 78, 80, 90, 99, 107, 116, 121, 127, 128, 130, 131, 133, 134, 136, 144-148] the remainder of studies did not report HIV prevalence among the enrolled population. Of the 22 studies reporting the prevalence of BCG vaccination among study populations, 10 studies reported a prevalence less than 50 percent,[67, 78, 128, 129, 134-137, 142, 149] and 12 studies reported a prevalence above 50 percent.[59, 77, 79, 80, 101, 104, 115, 125, 127, 131, 132, 154]

The pooled sensitivity for QFT-GIT was 0.81 (95% CI, 0.79 to 0.84; 48 studies; 7,055 participants; I^2=89.9%; **Table 2, Figure 5**). In stratified analyses, we found no meaningful differences in sensitivity estimates by country TB burden, HIV or BCG vaccination prevalence of the enrolled population, or timing of testing with respect to treatment (**Appendix F Figures 18–21**). Similar to studies reporting on T-SPOT.*TB* tests, stratified analyses were limited by a large number of studies that did not report information on key study characteristics. QFT-GIT assays returning indeterminate results among those with confirmed TB ranged from 0 percent[59, 67, 77, 106, 107, 119, 120, 134, 137, 139, 144-146, 148] to 19.4 percent[136] among studies explicitly reporting indeterminate results. The rest of the studies either did not have any persons with indeterminate results or excluded such persons from the analysis.

QFT-Gold Plus

The sensitivity of QFT-Gold Plus was reported in 11 studies.[106, 107, 116, 118-122, 124-126] Characteristics of studies are described in **Appendix D Table 2**. One study[124] was conducted among persons in a country with high TB burden, and eight studies[106, 107, 116, 120-122, 125, 126] were conducted among persons from countries with an intermediate TB burden. One study was conducted among persons in a low-TB-burden country.[119] One study was conducted among persons from a mix of low- and intermediate-TB-burden countries, including the United States.[118] In three studies, testing occurred prior to or no more than within 7 days of initiating TB treatment.[121, 124, 125] In five studies,[106, 107, 116, 118, 122] testing was performed no more than 8 to 14 days after TB treatment initiation. In one study, testing was performed either before treatment or no more than 30 days after TB treatment initiation,[126] and in two studies,[119, 120] the timing of

testing relative to the initiation of TB treatment was not reported. Among the three studies that allowed enrollment of persons living with HIV, the HIV prevalence ranged from 1.3 percent to 20 percent.[106, 118, 124] Three studies[107, 116, 121] did not enroll any persons living with HIV, and the prevalence of HIV was not reported in the remainder of studies. No studies reported BCG vaccination status among study participants.

The pooled sensitivity for QFT-Gold Plus was 0.89 (95% CI, 0.84 to 0.94; 11 studies; 939 participants; I^2=87.9%; **Table 2, Figure 6**). Stratified analyses by study characteristics previously described were limited by too few studies in each stratum for most analyses (**Appendix F Figures 22–24**). No studies using QFT-Gold Plus reported on indeterminate results.

Specificity of Screening Tests

TST

Twelve studies estimated specificity of TST using various thresholds for a positive test;[55, 57, 60, 62-66, 68, 69, 71, 73] study characteristics are described in **Appendix D Table 2**. Three studies reported specificity using a 5-mm induration threshold,[57, 62, 71] eight studies reported specificity using a 10-mm induration threshold,[55, 57, 62, 64, 68, 69, 71, 73] and 10 studies reported specificity using a 15-mm induration threshold.[55, 57, 60, 62, 63, 65, 66, 68, 69, 71] All studies were conducted in countries with a low TB burden, including nine in the United States.[55, 57, 60, 63, 65, 66, 68, 69, 73] In four studies, the HIV prevalence of the specificity population was reported to be 0 percent,[63, 64, 66, 73] and the remaining eight studies did not report HIV prevalence. In six studies, the prevalence of BCG vaccination was 0 percent;[60, 62-64, 68, 69] in three studies, the BCG vaccination prevalence ranged from 2 percent to 4 percent;[55, 57, 73] in one study where specificity subjects were Greek army recruits, all had been vaccinated with BCG;[71] and two studies did not report BCG vaccination prevalence.[65, 66]

The pooled estimate for specificity of TST was 0.95 (95% CI, 0.94 to 0.97; 3 studies; 5,149 participants) at the 5-mm threshold, 0.98 (95% CI, 0.97 to 0.99; 8 studies; 9,604 participants) at the 10-mm threshold, and 0.99 (95% CI, 0.98 to 0.99; 10 studies; 9,563 participants) at the 15-mm threshold (**Table 2, Figure 7**). These estimates were essentially unchanged from the prior report.

IGRA Tests

Four studies reported specificity data for IGRA tests; all were conducted in the United States. Two studies reported on T-SPOT.*TB*,[73, 155] two studies reported on QFT-GIT,[55, 141] and one study reported on QFT-Gold Plus.[123] Characteristics of these studies are described in **Appendix D Table 4**. BCG vaccination prevalence among three studies ranged from 0 percent to 3.5 percent and was not reported in the fourth study.[141] The prevalence for HIV was 0 percent in one study[73] and not reported in the other three studies.

The pooled estimates for specificity are summarized in **Table 2** and **Figure 7**. Analyses were limited by the small number of available studies reporting IGRA specificity data, which

precluded quantitative analyses for some tests. The two studies reporting on T-SPOT.*TB* reported specificities of 0.95 (95% CI, 0.91 to 0.97)[73] and 0.97 (95% CI, 0.96 to 0.98).[55] The pooled estimate for specificity of QFT-GIT was 0.99 (95% CI, 0.98 to 0.99; 3 studies; 2,090 participants). The specificity estimates of the lone study reporting specificity of QFT-Gold Plus was 0.98 (95% CI, 0.95 to 0.99).[123] The number of IGRA tests returning borderline or indeterminate results ranged 0 to 4.5 percent for studies reporting this information.

Reliability of Screening Tests

We did not identify any new studies reporting on the reliability of various screening tests for this update. The prior review identified nine studies of good or fair quality assessing the reliability of at least one of the included screening tests.[55, 68, 69, 75, 150-152, 156, 157]

Study Characteristics

Study characteristics are shown in **Appendix D Table 5**. Three studies assessed the interrater reliability of TST.[55, 68, 69] Two studies assessed the interrater reliability of T-SPOT.*TB*,[75, 156] one assessed the interrater reliability of QFT-GIT,[151] and one assessed the interlaboratory reliability of QFT-GIT.[150] Two studies assessed the test-retest reliability of T-SPOT.*TB* and QFT-GIT 1 to 4 weeks after an initial test.[152, 157, 158] Eight studies were conducted in countries with a low TB burden (7 in the United States and 1 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.[157] Two studies reported the percentage of the study population that had HIV; less than 1 percent in both studies were HIV positive.[152, 157] In two studies, the majority of participants were BCG vaccinated.[75, 157]

Results

Interrater reliability. Three studies (N=1,826,[55] N=1,189,[68] and N=127[69]) 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 vs. 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.[156] One study (N=146) assessed interrater reliability for manual vs. 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.[151] 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).[151]

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.[150] 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.[150]

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*.[152] Two studies measured the test-retest reliability of QFT-GIT. One study enrolled U.S. healthcare workers,[152] and one enrolled a population from a country with a high TB burden (Nepal).[157, 158] In the study (N=130) enrolling healthcare 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.[152] 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, 0.50 to 0.83) for T-SPOT.*TB*.[157]

KQ 2b. What Are the Accuracy and Reliability of Sequential Screening Strategies That Use TST and IGRA in Asymptomatic Adults Who Are at Increased Risk for Developing Active TB Disease, Including Among Specific Populations of Interest?

We found no eligible studies that addressed this question.

KQ 3. What Are the Benefits of Treatment for LTBI With CDC-Recommended Pharmacotherapy Regimens, Including Among Specific Populations of Interest?

We included five RCTs[159-163] that assessed treatment of LTBI and met all eligibility criteria (**Appendix D Table 6**) and one network meta-analysis.[164] One compared INH with placebo, two compared RIF with INH, and two compared RPT plus INH with INH alone. Two of the articles describing RCTs[161, 163] and the network meta-analysis[164] were new in this update.

We identified four additional RCTs[165-168] that compared INH with placebo that did not meet all eligibility criteria but were used in sensitivity analyses (**Appendix D Table 7**). These were included in the prior report for the USPSTF, and we did not identify new studies to add to this sensitivity analysis. 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 (i.e., ≥1 year of INH), and some used lower or higher doses than currently recommended or did not require LTBI confirmation for subjects to be eligible. One of the four trials was rated poor quality for high risk of selection bias, attrition bias, confounding, and measurement bias.

The prior report on this topic and our update searches identified additional RCTs (e.g., that compared INH with placebo), which we excluded from this review. Reasons for excluding studies from this review are listed in **Appendix C**. Reasons for excluding studies from the prior report are listed in the Appendix of the prior report. For example, several trials focused on the use of INH among household contacts of active TB cases but did not require LTBI confirmation for study entry, some enrolled a large proportion of children, some evaluated ineligible populations (e.g., persons with silicosis), some evaluated 1 year or more of INH treatment, and some used doses not currently recommended by the CDC.[169-173] Two other trials randomized households or villages in Greenland[174] or Alaska[175] for the purpose of evaluating the prophylactic use of INH. Greenland and Alaska both had a high prevalence of active TB at the time of the study. These two trials did not require LTBI confirmation for study entry. One of them evaluated an unusual isoniazid regimen (400 mg for 3 months, nothing for 3 months, then 400 mg for 3 months);[174] the other evaluated 1 year of INH and included many children.[175]

INH Compared With Placebo

The International Union Against Tuberculosis (IUAT) trial was the single trial meeting all eligibility criteria that compared INH with placebo.[159] It was included in the prior review for the USPSTF. It randomized 27,830 adults from seven European countries with fibrotic pulmonary lesions but not active TB or previous antituberculosis treatment to four groups: INH 300 mg daily for 12 weeks, INH 300 mg daily for 24 weeks, INH 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 8**). The relative risks (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. For the 24-week CDC-recommended regimen (among the current CDC alternative regimens), we calculated a number needed to treat of 112 to prevent one 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%) (**Appendix F Figure 25**).

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 INH 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 INH 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 INH groups compared with placebo, respectively.

RIF Compared With INH

We included two RCTs making this comparison. The first was an open-label Phase 2 clinical trial (Menzies 2008) conducted in Canada, Brazil, and Saudi Arabia that randomized 847 participants to 4 months of RIF or 9 months of INH to compare adverse events and treatment completion.[161] 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 RIF group and one in the INH group.

The second article was new in this update (Menzies 2018) and was conducted by the same primary author. It was an open-label, Phase 3 clinical trial completed in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea.[161] It randomized 6,063 participants to 4 months of RIF (now a CDC-preferred regimen, strong recommendation) or 9 months of INH (now an alternative CDC regimen). The primary objective was to compare the rates of confirmed active TB in the two groups. Participants included were at increased risk of progression to active TB. Most had a history of close contact (70.7%) or casual contact (12.4%) with an active TB case; fewer had HIV (4.0%) or an immunosuppressive condition (3.2%). Over 95 percent of participants randomized completed 28 months of followup. In the INH group, nine participants developed active TB compared with eight in the RIF group. This total does include patients who progressed to active TB in the Phase 2 clinical trial completed by the same authors. The RIF therapy was found to be noninferior to the INH, but not superior.

RPT Plus INH Compared With INH Alone

Two of the included RCTs made this comparison. The first, the PREVENT TB study (Sterling 2011[162]), was included in the prior report for the USPSTF and 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 RPT (900 mg) plus INH (900 mg) for 3 months or to daily self-administered INH (300 mg) for 9 months.[162] 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 INH-only group. The combination therapy group was found to be noninferior to the INH-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 persons. For this subset, active TB developed in five persons in the combination therapy group and in 10 persons in the INH-only group. The combination therapy group was found to be noninferior to the INH-only group. Overall mortality was similar for the two groups (30 vs. 34 deaths, respectively; p=0.42).

The second RCT (Sun 2018), new in this update, was an open-label multicenter trial completed in Taiwan that randomized 283 participants (263 of those were included in analyses) age 12 years or older to either 3 months of once-weekly directly observed RPT plus INH or 9 months of daily directly observed INH alone.[163] The endpoints were treatment completion and incidence of severe adverse drug reactions, so this study is discussed in more detail in the KQ 5 results. However, it did report zero deaths from either TB or all-cause mortality in either group.

Previously Published Network Meta-Analysis

The network meta-analysis (53 included studies) used a mixed-treatment comparison methodology focused on two prespecified endpoints: prevention of active TB (covered in KQ 3) and hepatotoxicity (covered in KQ 5).[164] It found that the shorter-duration recommended regimens are efficacious for preventing active TB (e.g., rifampicin for 3 to 4 months, RPT plus INH combination, INH for 6 months) and may have fewer adverse effects and higher completion rates.[164] 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 were taking immunosuppressive biologic medication, which are all populations excluded from the present review. The network meta-analysis also included treatment regimens not eligible for our review. For prevention of active TB, it reported that multiple regimens were efficacious compared with placebo or no treatment, including INH regimens of 6 months (odds ratio [OR], 0.65 [95% credible interval {CrI}, 0.50 to 0.83] vs. placebo) or longer, rifampicin-INH regimens of 3 to 4 months (OR, 0.53 [CrI, 0.36 to 0.78] vs. placebo), and weekly RPT-INH regimens (OR, 0.36 [CrI, 0.18 to 0.73] vs. no treatment). The network meta-analysis also noted that it found no conclusive evidence that HIV status altered treatment efficacy.

KQ 4. Are Harms Associated With Screening for LTBI, Including Among Specific Populations of Interest?

KQ 4a. Do These Harms Differ by Screening Method or Strategy?

KQ 4b. Do These Harms Differ by Population?

We found no eligible studies that addressed this question.

KQ 5. What Are the Harms Associated With Treatment of LTBI With CDC-Recommended Pharmacotherapy Regimens, Including Among Specific Populations of Interest?

We included nine RCTs (described in 11 articles) and one network meta-analysis assessing harms associated with the treatment of LTBI that met eligibility criteria (**Appendix D Tables 6 and 9**).[159-164, 176-181] Among the RCTs, one compared INH with placebo,[159] four compared RIF with INH (although participants of the Menzies [2008] Phase 2 trial were included in the Menzies [2018] Phase 3 trial),[160, 161, 177, 178] two compared RPT plus INH with INH alone,[163, 179] one compared RIF plus INH to RPT plus INH,[180] and one compared weekly RPT plus INH with twice-weekly RPT plus INH.[181] Four of the RCTs (described in 6 articles, including 2 post hoc analyses of previously included trials) and the network meta-analysis were new in this update.[161, 163, 176, 179-182]

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. The criteria for RCTs to be included in sensitivity analyses for KQ 5 were 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 (i.e., ≥1 year of INH), one used a shorter duration than is currently recommended by the CDC (3 months of INH), and some used a lower dose than currently recommended or did not require LTBI confirmation for subjects to be eligible. We rated two of these trials as fair quality and the other three as poor quality.

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, as rates of treatment discontinuation due to GI events in another study, and by separate types of GI events (i.e., nausea, clay-colored stools, or anorexia) with no summary rate in another study.

INH Compared With Placebo

The IUAT trial was the single trial meeting all eligibility criteria that compared INH with placebo.[159, 183] 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 9**).[159] The RRs for developing hepatotoxicity associated with INH 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 (**Appendix F Figure 26**). For the

study arms comparing the 24-week CDC-approved regimen with placebo (N=13,955), we calculated that one case of hepatotoxicity would result from treating 279 persons with INH (i.e., a number needed to harm [NNH] of 279). Our sensitivity analyses using data from the IUAT trial (3 treatment arms combined) and three additional RCTs, 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 F Figure 27**).[184-186]

The one RCT included in the main analysis (i.e., the IUAT trial) comparing INH with placebo for treatment of LTBI reported mortality rates from hepatotoxicity of 0.03 percent, 0.0 percent, and 0.01 percent for the 12-, 24-, and 52-week INH 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 INH was 0.14 deaths per 1,000 persons receiving INH, 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 INH treatment groups combined. A total of 345 patients (1.8%) receiving INH 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 INH vs. 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, including a total of 55,398 participants, found an RR of 1.58 (95% CI, 1.00 to 2.49) (**Appendix F Figure 28**).[165, 167, 186]

GI Adverse Events

The IUAT trial reported that 1.2 percent of INH patients and 0.9 percent of placebo patients discontinued treatment due to GI distress (RR, 1.33 [95% CI, 1.01 to 1.75]).[183] Among studies included in sensitivity analyses, one reported GI adverse events (0.7% in INH group vs. 0.3% in placebo group) and one reported nausea (3.3% in INH group vs. 1.7% in placebo group), clay-colored stools (10.0% in INH group vs. 5.0% in placebo group), and anorexia (8.3% in both INH and placebo groups).[165, 186]

Other Harms

No other adverse events were reported in the IUAT trial. A variety of other adverse events were reported in the RCTs included in sensitivity analyses. Rates of other adverse events were generally similar among INH and placebo patients (**Appendix D Table 9**). One study reported an increased risk for rash (0.9% of INH patients and 0.3% of placebo patients; RR, 2.7 [95% CI, 1.27 to 5.73]).[166, 168]

INH Compared With RIF

We included four open-label RCTs that compared RIF with INH (**Appendix D Table 6**).[160, 161, 177, 178] Additionally, a post hoc safety analysis of two of these RCTs was included. [176] One trial conducted in Canada (N=116) compared 4 months of RIF (10 mg/kg of body weight, up to 600

mg/day) with 9 months of INH (5 mg/kg, up to 300 mg/day).[177] A later Phase 2 trial by the same authors conducted in Canada, Brazil, and Saudi Arabia randomized 847 participants to the same two treatments.[160] A third study (a Phase 3 trial, new in this update) by the same authors conducted in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea (N=6,063) compared the same treatments.[161] In all three studies, participants were age 18 years or older with documented LTBI. Adverse event data for the second and third studies were reported together (i.e., the Phase 3 trial included some data from the Phase 2 trial). Over half of the participants in the first two studies were male, but the third study included a greater proportion of females. The fourth trial randomized inmates (N=364) in the San Francisco City and County Jail diagnosed with LTBI at jail entry to 9 months of INH (900 mg twice per week) or 4 months of RIF (600 mg/day). Ninety-three percent of study participants were male.[178]

Hepatotoxicity

All four RCTs presented hepatotoxicity data; one trial combined its data with the data from an earlier study by the same authors. Rates of hepatotoxicity in these RCTs among patients receiving INH were 5.2 percent,[177] 1.9 percent,[161] and 11.4 percent.[178] Rates of hepatotoxicity among RIF-treated patients were 0.0 percent, 0.3 percent, and 4.4 percent, respectively. Our meta-analysis of three RCTs (total N=7,339) found a greater risk of hepatotoxicity for patients treated with INH than for those treated with RIF (RR, 4.22 [95% CI, 2.21, 8.06]; I^2=28.7%) (**Appendix F Figure 29**). All studies reported zero deaths from hepatotoxicity.

Treatment Discontinuation Because of Adverse Events

Rates of discontinuation because of adverse events were reported in all four included RCTs, but one trial combined its data with the data from an earlier Phase 2 study by the same author. Rates were 13.8 percent (INH) and 3.4 percent (RIF),[177] 2.3 percent (INH) and 0.9 percent (RIF),[161] and 0.0 percent (INH) and 1.1 percent (RIF).[178] Our meta-analysis found no statistically significant difference between treatments (RR, 2.25 [95% CI, 0.90 to 5.59]; I^2=35.2%; N=7,339) (**Appendix F Figure 30**).

GI Adverse Events

Among the four included RCTs, one reported GI adverse events in 3.4 percent of the study population, not separated by treatment arm.[177] One, which includes the data from two of these RCTs, reported GI intolerance of 0.03 percent among patients treated with INH and 0.09 percent among those treated with RIF (calculated RR: 0.34 [95% CI, 0.03, 3.23]).[161] The third study reported more GI adverse events among patients treated with INH than with RIF (calculated RR: 1.16 [95% CI, 0.62 to 2.19]).[178]

Other Harms

The four RCTs in the main analysis reported on various other harms, including hematologic, drug interactions, and rash. The post hoc safety analysis reviewing two of these RCTs found a total of 199 adverse events due to the study drugs, and 68 (34.2%) of these were in the RIF arms and 131 (65.8%) in the INH arms.[176] In the RIF arm, 1.5 percent of participants experienced a

Grade 1–2 rash or any Grade 3–5 adverse events, compared with 2.7 percent of participants in the INH arm.

RPT Plus INH Compared With INH Alone

Two included RCTs made this comparison, as well as one companion trial that provided a more detailed review of systemic drug reactions (SDRs).[162, 163, 179] The PREVENT TB study (included in the 2016 review for USPSTF) 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 RPT at 900 mg plus INH at 900 mg for 3 months or to daily self-administered INH at 300 mg for 9 months.[162] More details regarding this study are presented in the results section on benefits of treatment (KQ 3). A post hoc analysis was later completed to examine the participants with SDRs.[179] One study site was excluded from the SDR analysis because of discrepancies regarding receipt of study drug and DOT.

The second RCT was an open-label multicenter trial completed in Taiwan that randomized 263 participants age 12 years or older to either 3 months of weekly directly observed RPT 15 mg/kg plus INH 15 mg/kg (3HP) or 9 months of daily directly observed INH 5 mg/kg alone (9H).[163] All subjects had close contact with an active TB case and had a positive TST within 1 month after exposure. The mean age was 32 years and 58 percent of the subjects were male. Participants who completed treatment were followed for an additional 2 years. The endpoints evaluated were treatment completion and incidence of severe adverse drug reactions. Compared with the 9H regimen, the 3HP regimen had a higher completion rate with lower hepatotoxicity rates but higher rates of SDRs.

Hepatotoxicity

Both studies reported hepatotoxicity data, but one reported these data based on elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), while the other reported hepatotoxicity as a severity grade. Rates of Grade 3 and 4 hepatotoxicity in the PREVENT TB study were 4.9 percent and 1.0 percent in the RPT plus INH arm and 5.5 percent and 1.1 percent in the INH-only arm.[162] The RR for Grade 3 or 4 hepatotoxicity was 0.90 (95% CI, 0.75 to 1.08). The post hoc analysis completed by the same authors found a total of 114 cases of hepatotoxicity attributable to the study drug in the PREVENT TB study, with 17 of these in the RPT plus INH arm (0.43% of those who received 3HP) and 97 in the INH arm (2.70% of those who received 9H) (RR, 0.16 [95% CI, 0.10 to 0.28]).[179]

The trial conducted in Taiwan reported elevations of AST and ALT greater than 3 times the upper limit of normal in 4.5 percent of the RPT plus INH group and in 9.9 percent in the INH-alone group (RR, 0.46 [95% CI, 0.18 to 1.17]) and reported clinically relevant hepatotoxicity in 1.5 percent vs. 5.3 percent (RR, 0.28 [95% CI, 0.06 to 1.34]).

The trial conducted in Taiwan reported zero deaths from hepatotoxicity in either group.

Treatment Discontinuation Because of Adverse Events

Both studies reported on discontinuation due to adverse events. Rates of discontinuation because of adverse events were higher in the RPT plus INH arms in both studies (5.2% and 9.1% in PREVENT TB and the trial conducted in Taiwan, respectively) than in the INH-only arms (4.1% and 5.3%) (RR, 1.28 [95% CI, 1.03 to 1.59] in PREVENT TB and RR, 1.70 [95% CI, 0.69 to 4.19] in the trial conducted in Taiwan).

GI Adverse Events

The trial conducted in Taiwan reported on GI adverse events. Overall, 21.2 percent of subjects in the RPT plus INH arm experienced GI adverse events compared with 12.2 percent of the subjects in the INH-alone group (RR, 1.74 [95% CI, 0.99 to 3.05]). Specific side effects included abdominal pain (3.0% vs. 2.3%; RR, 1.32 [95% CI, 0.30 to 5.80]), diarrhea (1.5% vs. 2.3%; RR, 0.66 [95% CI, 0.11 to 3.90]), nausea (9.1% vs. 6.9%; RR, 1.32 [95% CI, 0.58 to 3.03]), and vomiting (7.6% vs. 0.8%; RR, 9.92 [95% CI, 1.29 to 76.4]).

Other Harms

The studies evaluated various other harms, including possible hypersensitivity, SDR, and flu-like symptoms. Possible hypersensitivity was reported in 4.1 percent of INH plus RPT patients and 0.5 percent of INH-only patients in the PREVENT TB study.[5] The RR of possible hypersensitivity for RPT plus INH vs. INH-only patients was 8.04 (95% CI, 4.88 to 13.26).

Among the 7,552 participants who received at least one dose of the study drugs in the PREVENT TB study, 153 had a clinically significant SDR attributed to study drugs. The post hoc analysis of PREVENT TB reviewed the 153 SDRs and found that 138 were in the RPT plus INH arm vs. 15 in the INH-only arm (RR, 8.7 [95% CI, 5.1 to 14.7]). Of the 138, presentations of symptoms included flu-like (n=87, 63%), cutaneous (n=23, 17%), GI (n=7, 5%), respiratory (n=5, 4%), and not defined (n=16, 12%). Thirteen of these events were severe with four resulting in hospitalization. In the INH-only arm, SDRs included cutaneous (n=9, 60%), flu-like (n=2, 13%), GI (n=1, 7%), and not defined (n=3, 20%). One of these events was severe and resulted in hospitalization. None of the participants who developed an SDR completed study treatment.

The trial conducted in Taiwan reported SDRs in 3.8 percent of the RPT plus INH participants and 0 percent of the INH-only participants (RR, 10.9 [95% CI, 0.6 to 195.5]). It also reported flu-like symptoms in 40.1 percent of the RPT plus INH participants and 16.8 percent of the INH-only group. Adverse drug reactions aside from hepatotoxicity occurred in 49.2 percent of the RPT plus INH group and 25.2 percent of the INH-only group.

RIF Plus INH Compared With RPT Plus INH

The single study, the HALT LTBI pilot study, that made this comparison was an open-label pilot RCT completed at two TB clinics in London that randomized 52 participants ages 16 to 65 years with LTBI to self-administered RIF plus INH daily for 90 days or RPT plus INH weekly for 12 weeks.[180] The mean age of subjects within these groups was 32.5 years and 38.2 years,

respectively, and 50 percent were male. Participants were followed for a total of 16 weeks to evaluate the primary outcome of treatment completion. The only specific harms reported by this study were related to hepatotoxicity. Elevated ALT or AST (defined as above the normal range) was reported in four participants (16%) in the RIF plus INH group and in three participants (11%) in the RPT plus INH group. There were zero deaths from hepatotoxicity in the study, but one participant (4%) in the rifampicin plus INH arm was withdrawn from the trial due to liver function tests greater than 3 times the upper limit of normal accompanied by symptoms of hepatotoxicity.

RPT Plus INH Compared With RPT Plus INH

The one included study making this comparison was an open-label trial conducted in China that randomized 3,738 persons ages 50 to 69 years to directly observed once-weekly INH up to 900 mg and RPT up to 900 mg for 12 weeks (the 3HP regimen), directly observed twice-weekly INH up to 600 mg and RPT up to 600 mg for 8 weeks (the $2H_2P_2$ regimen), or to an untreated control group.[181] Among randomized subjects, 45 percent were female. Because of the high incidence of adverse events in the study, the 3HP regimen was shortened to 8 weeks, and the $2H_2P_2$ regimen was shortened to 6 weeks. The trial reported hepatotoxicity, discontinuation because of adverse events, GI adverse events, hypersensitivity or allergy events, and flu-like symptoms.

Hepatotoxicity, defined as AST or ALT elevated more than 3 times the upper limit of normal along with accompanying symptoms or AST or ALT elevated more than 5 times the upper limit of normal without symptoms, occurred in 13 participants (1.02%) in the 3HP group and 15 participants (1.17%) in the $2H_2P_2$ group (p=0.704) (RR, 0.88 [95% CI, 0.42 to 1.84]). There were zero deaths from hepatotoxicity and no deaths attributed to LTBI treatment. The discontinuation rate due to adverse events was similar in the two treatment arms of the study (77 vs. 82 participants, 6.0% vs. 6.3%, RR, 0.95 [95% CI, 0.70 to 1.28]). The rate of GI adverse events was significantly higher in the 3HP group than in the $2H_2P_2$ treatment group (110 vs. 66 participants; 8.6% vs. 5.2%, p=0.006; RR, 1.69 [95% CI, 1.26 to 2.27]) as were influenza-like symptoms (46 vs. 29 participants; 3.6% vs. 2.3%; RR, 1.60 [95% CI, 1.01 to 2.54]), whereas hypersensitivity or allergy events were less common in the 3HP group than in the $2H_2P_2$ group (43 vs. 65 participants; 3.4% vs. 5.1%; RR, 0.67 [95% CI, 0.46 to 0.98]).

Meta-Analysis Comparison

The network meta-analysis used a mixed-treatment comparison methodology and focused on two prespecified endpoints: prevention of active TB (covered in KQ 3) and hepatotoxicity (covered in KQ 5). The meta-analysis found greater odds of hepatotoxicity with longer duration of therapy and regimens containing INH only (OR vs. no treatment [95% CrI]: INH 6 months, OR 1.10 [0.40, 3.17]; INH 9 months, OR 1.70 [0.35, 8.05]; INH 12 to 72 months, OR 2.72 [0.96, 7.44]) than with other regimens currently recommended by the CDC (OR vs. no treatment [95% CrI]: INH plus RPT, 0.52 [0.13, 2.15], RIF 3 to 4 months 0.14 [0.02 to 0.81], INH plus RIF 3 to 4 months, 0.72 [0.21, 2.37]).[164] Although data on hepatotoxicity were limited, CrIs were wide (estimates were imprecise), and findings were based on relatively few events. 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 were 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. The authors noted that stratifying hepatotoxicity results by HIV status, immunosuppression, and TB incidence did not affect the conclusions.

Chapter 4. Discussion

Summary of Evidence

Table 3 provides a summary of the main findings in this evidence review organized by KQ along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability. This review did not find evidence on whether results differ for specific populations defined by age, sex, pregnancy, or race/ethnicity. Applicability of the findings to specific populations at higher risk for TB is described below in the sections on accuracy of screening tests and treatment of LTBI.

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. Therefore, the strength of evidence was graded as insufficient for KQs 1 and 4.

Accuracy and Reliability of Screening Tests

The lack of tests for the direct diagnosis of LTBI necessitates that evaluating the accuracy of screening tests relies on extrapolation from studies of persons with active, confirmed TB (sensitivity) or healthy persons without TB risks and exposures (specificity). The evidence suggests that for the populations and settings studied, currently available tests are moderately sensitive and highly specific. Previously published systematic reviews evaluating accuracy of screening tests for LTBI, including our prior review for the USPSTF,[187] are generally consistent with our findings.[188-191] The applicability of the evidence to primary care practice settings and populations is somewhat uncertain because the lack of a direct test for LTBI requires screening test accuracy studies to be conducted in specific populations (e.g., populations with active, confirmed TB for estimates of sensitivity). Nevertheless, it seems reasonable to assume applicability to primary care practice settings that serve high-risk populations (e.g., clinics serving persons who had temporary or permanent residence in a country with a high TB rate), where the use of a highly specific test among a higher prevalence population minimizes false positives and a moderately sensitive test (conducted after it is indicated by a clinical risk assessment) can help determine the likelihood of infection to inform treatment decisions.

Benefits and Harms of Treatment of LTBI

The best evidence on effectiveness of pharmacotherapy with a CDC-recommended regimen versus placebo is from the IUAT trial (N=27,830). It enrolled subjects with pulmonary fibrotic lesions, a group thought to be at the highest risk for progression to active TB, and it reported that participants with smaller lesions progressed to active TB at lower rates than those with larger

lesions. In addition, the treatment studies used in our sensitivity analysis did not enroll populations that were identified to have LTBI via screening in primary care settings; rather, they were household contacts of active cases,[165] veterans with inactive pulmonary TB,[166, 184] persons residing in mental institutions,[167] and military members exposed to an active TB case.[168] Thus, the available evidence has uncertain applicability to persons in primary care settings who screen positive on the TST or IGRA but have normal chest X-rays or who are not recent converters or close contacts. Therefore, estimates of treatment effectiveness may represent the upper bounds of effectiveness. When assessing applicability of the evidence comparing INH with placebo, we note that the trials were published more than 40 years ago (1963, 1965, 1968, 1978, and 1982) and treatment of LTBI has been the standard of care for decades. More current data for estimating effectiveness were not available. It is unclear whether changes in the prevalence of TB (which has decreased), treatments for active TB, or likelihood of LTBI progressing to active TB would significantly change estimates of effectiveness. Trials comparing INH with placebo mostly evaluated longer durations of treatment (e.g., 1 year of isoniazid) because longer durations were recommended at the time. After INH had established effectiveness, subsequent studies evaluated shorter durations of treatment and other regimens (compared with standard INH regimens) and were generally focused on harm reduction, improving adherence, or both. Early studies of INH indicated a four- to five-fold increase in hepatotoxicity compared with placebo, although deaths because of hepatotoxicity were very rare—a total of three participants in IUAT, all of whom had continued to take INH after liver abnormalities were recognized. Subsequent head-to-head trials and network meta-analyses indicated noninferiority, improved adherence, and lower risk of hepatotoxicity for current CDC-preferred LTBI treatments (rifampin, INH plus rifapentine, and INH plus rifampin) than with INH alone.

Limitations

Our review had limitations. First, it did not cover testing of close contacts of persons with active TB (usually managed by public health programs) or high-risk populations for whom LTBI testing is considered part of standard disease management (e.g., persons with HIV, persons with planned or active use of tumor necrosis factor-alpha inhibitors or other targeted immune modulators). Next, we did not evaluate cost-effectiveness. A 2011 publication estimated the incremental cost-effectiveness of screening for LTBI as cost saving for IGRA compared with TST and as $100,000 per quality-adjusted life year (QALY) gained for IGRA compared with no screening for persons born outside the US.[192] A 2017 publication reported that screening for and treating LTBI among persons born outside the US is likely cost-effective except among persons with end-stage renal disease (because of competing risks of death).[193] A 2020 publication found that the cost-effectiveness of targeted screening for and treatment of LTBI varied significantly across populations and states,[194] likely attributable to differences in prevalence of TB and risk factors for LTBI from region to region. Testing and treatment consistently prevented the most TB cases for persons born outside the US.[194] Next, there is uncertainty about the applicability of studies conducted outside of the United States. For example, differences in healthcare and social services systems could potentially influence study results through availability of support (or lack thereof) for following up to have TSTs assessed or access to DOT. Incorporation of country TB burden in our eligibility criteria, results, and analyses served as a proxy for some applicability issues in that realm. Finally, we did not identify eligible studies focused on pregnant women.

Some studies of potential harms of LTBI treatment among pregnant women that were not eligible for our review (e.g., because all participants were persons living with HIV) may help to inform treatment decisions for pregnant women. For example, a retrospective cohort study of almost 44,000 women on antiretroviral therapy for HIV in South Africa compared outcomes for the 7,310 who received 6 to 12 months of INH 5 mg/kg/day (per national guidelines for TB prevention in persons living with HIV) with the others who did not and found improved pregnancy outcomes for those taking INH, including decreased miscarriage and stillbirth.[195] In addition, analysis of data from the PREVENT TB and iAdhere trials of pregnant women inadvertently exposed to either INH or rifapentine found no increase in fetal loss or congenital anomalies.[196] The current joint guidelines from the American Academy of Pediatrics and the American College of Obstetrics and Gynecology recommend screening for latent TB in early pregnancy for women at high risk for TB, including recent TB exposure, HIV infection, risk factors increasing risk of progression to active disease (e.g., cancer), use of immune-suppressing drugs such as tumor necrosis factor-alpha inhibitors or chronic steroids, renal failure on dialysis, homelessness, living or working in long-term care facilities such as nursing homes and prisons, being medically underserved, and being born in a country with high prevalence of TB.[197]

Future Research Needs

While progress toward the public health goal of TB elimination in the United States continues, future research could potentially improve programs that screen for and treat LTBI. Research that informs our understanding of the incremental net benefit of more or less frequent screening could help determine optimal approaches to screening. Future research on the optimal approaches for identifying appropriate candidates for LTBI screening (i.e., risk assessment tools to identify persons at sufficiently high risk) could improve screening programs. For example, operations research could evaluate efficient ways to identify persons with risk factors that warrant screening within low-prevalence primary care settings. Such settings may have more challenges with implementing screening for LTBI than specialized clinics that care for high-risk populations and therefore commonly screen for LTBI (e.g., prison clinics, clinics serving large proportions of persons born outside the US). Further, development of tests or approaches that are able to identify which persons with LTBI will or will not develop active TB disease would optimize efficiency of LTBI treatment and reduce unnecessary harms, for example, from treating persons who would never have developed active TB and exposing them to potential adverse drug effects and the socioeconomic disruptions of taking a medication and the required, related monitoring.

Future research on new pharmacotherapy regimens or even shorter treatment durations could potentially identify treatment regimens that would further optimize benefits and adherence while further limiting harms. The BRIEF (Brief Rifapentine-Isoniazid Efficacy for TB) trial found 1 month of INH plus rifapentine to be noninferior to 9 months of INH for a composite outcome of progression to TB or death from TB or unknown causes among persons living with HIV.[198] Completion of therapy was also greater for the 1-month regimen. The 1-month regimen is not listed in the CDC recommendations, although it is listed as an alternative choice in the WHO guidelines. The regimen has not been studied in persons without HIV. The BRIEF trial participants were eligible if they were from an area with a high prevalence of TB or if they had evidence of LTBI; of those enrolled, only 23 percent had a positive TST or IGRA.

Conclusion

No studies evaluated the benefits and harms of screening for LTBI compared with no screening. TST and IGRAs are moderately sensitive and highly specific. Treatment of LTBI with recommended regimens reduces the risk of progression to active TB. INH is associated with higher rates of hepatotoxicity than placebo or rifampin.

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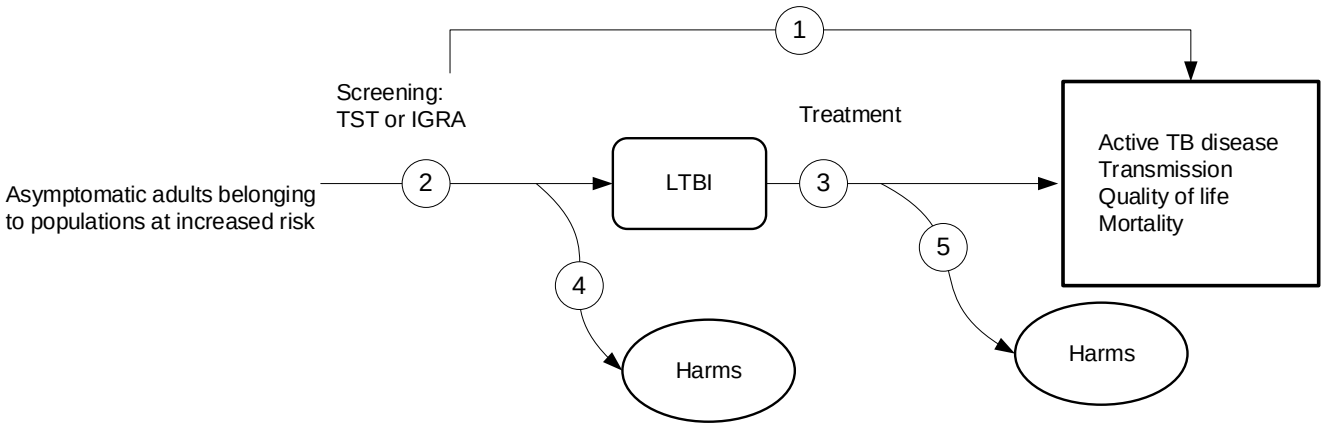
Figure 1. Analytic Framework



Abbreviations: IGRA=interferon-gamma release assay; LTBI=latent tuberculosis infection; TB=tuberculosis; TST=tuberculin skin test.

Figure 2. Summary of Evidence Search and Selection

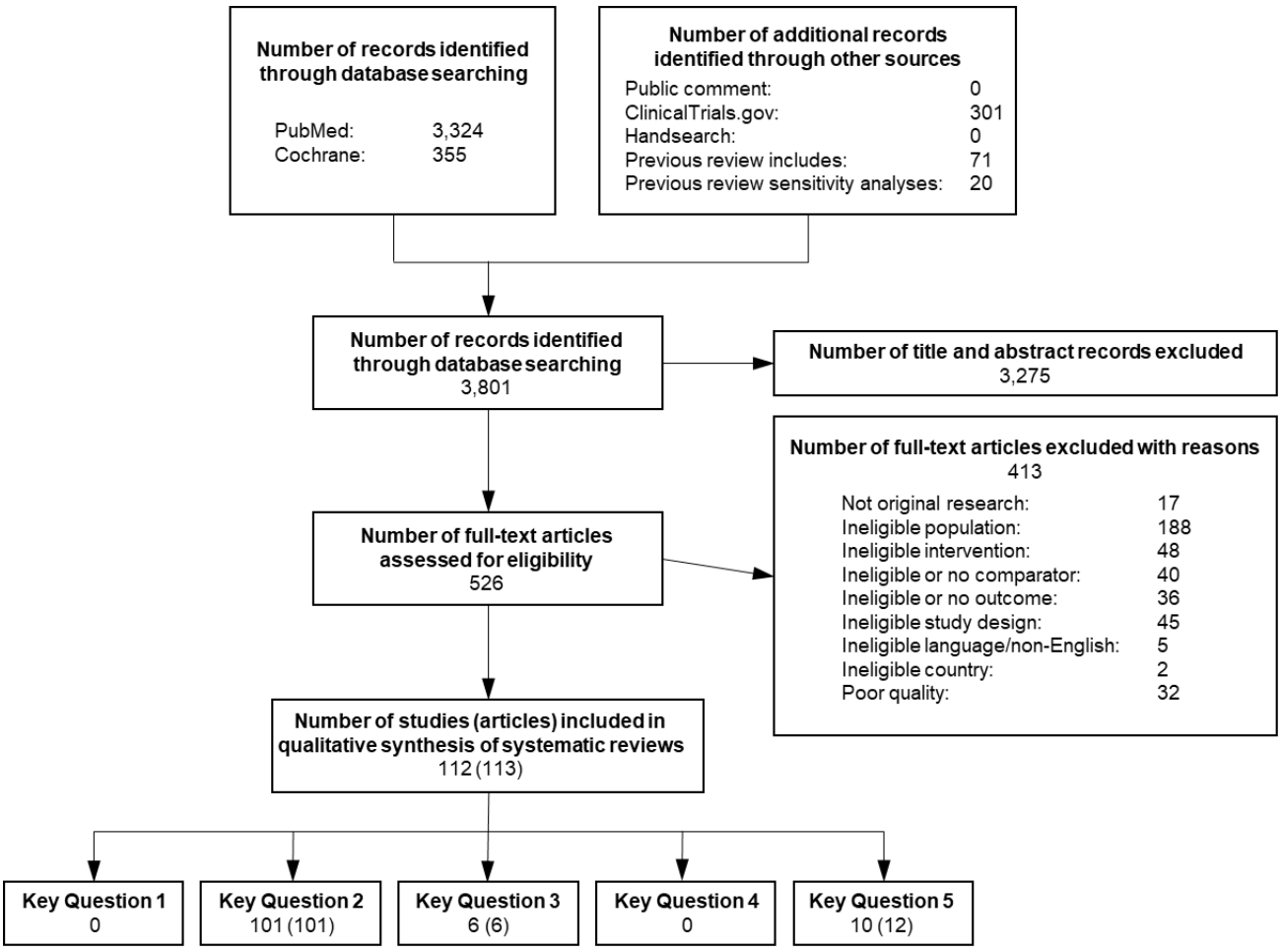
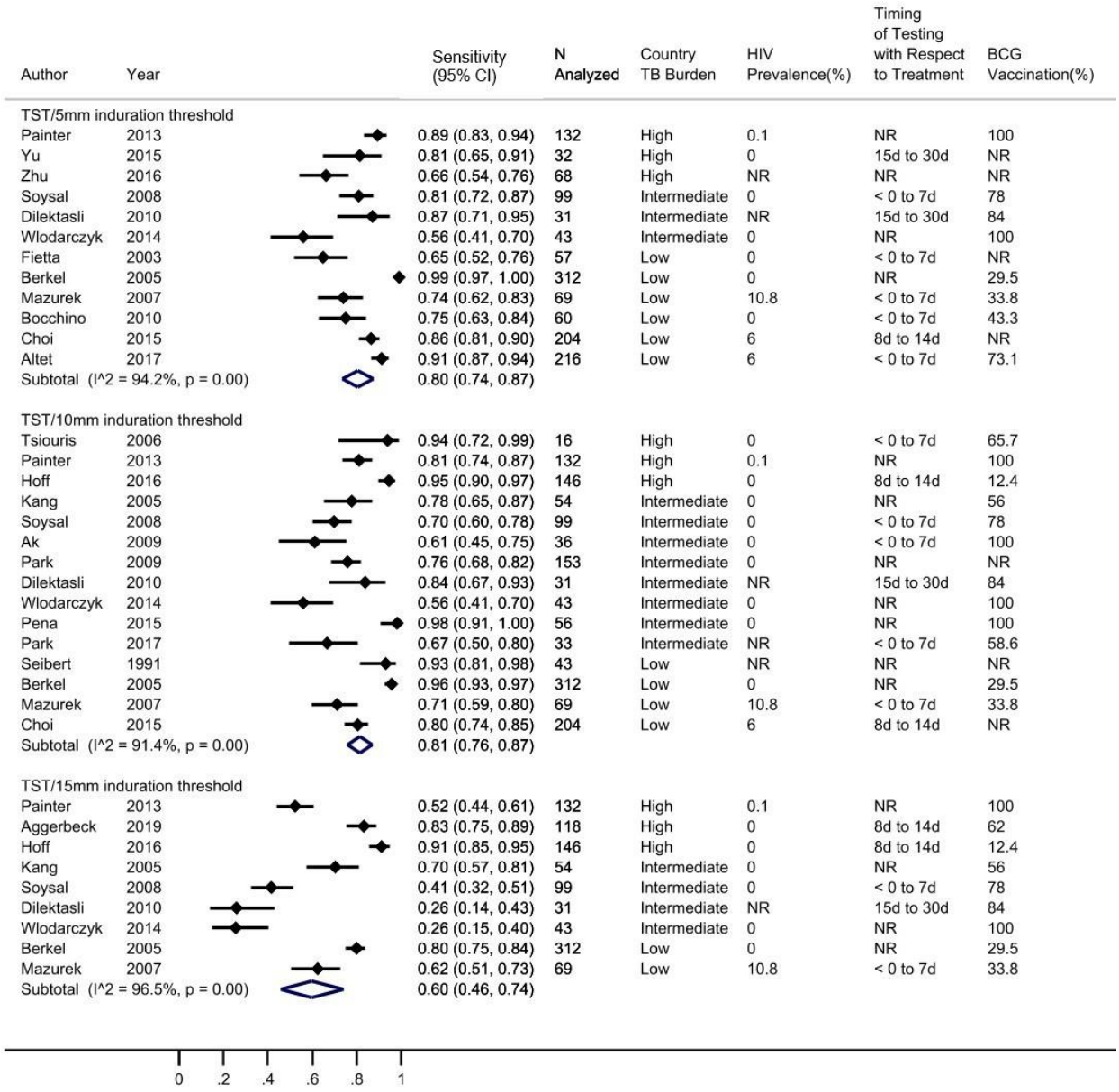
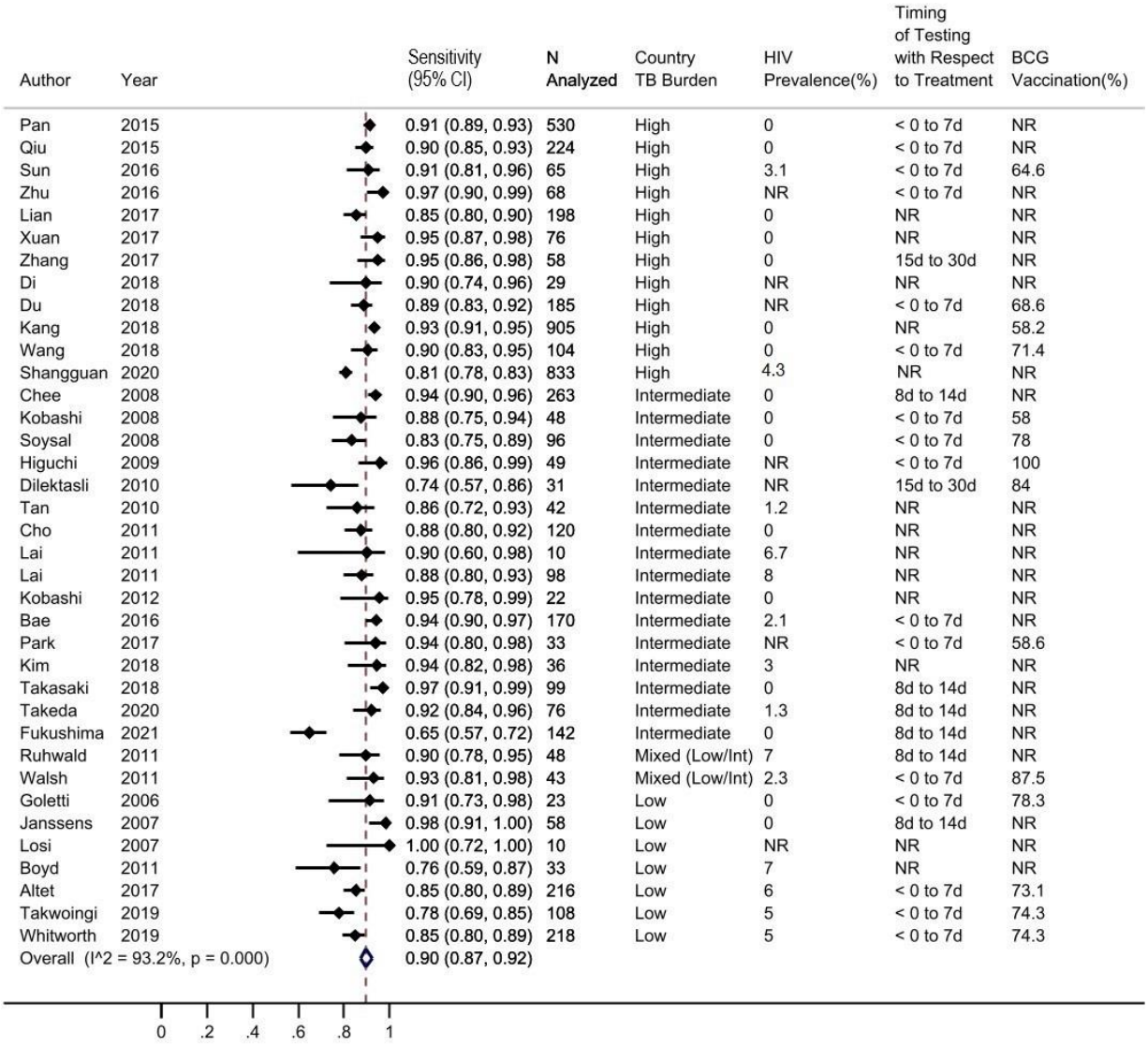


Figure 3. Individual Study and Pooled Estimates of Sensitivity for Various Thresholds of the TST for TB Infection



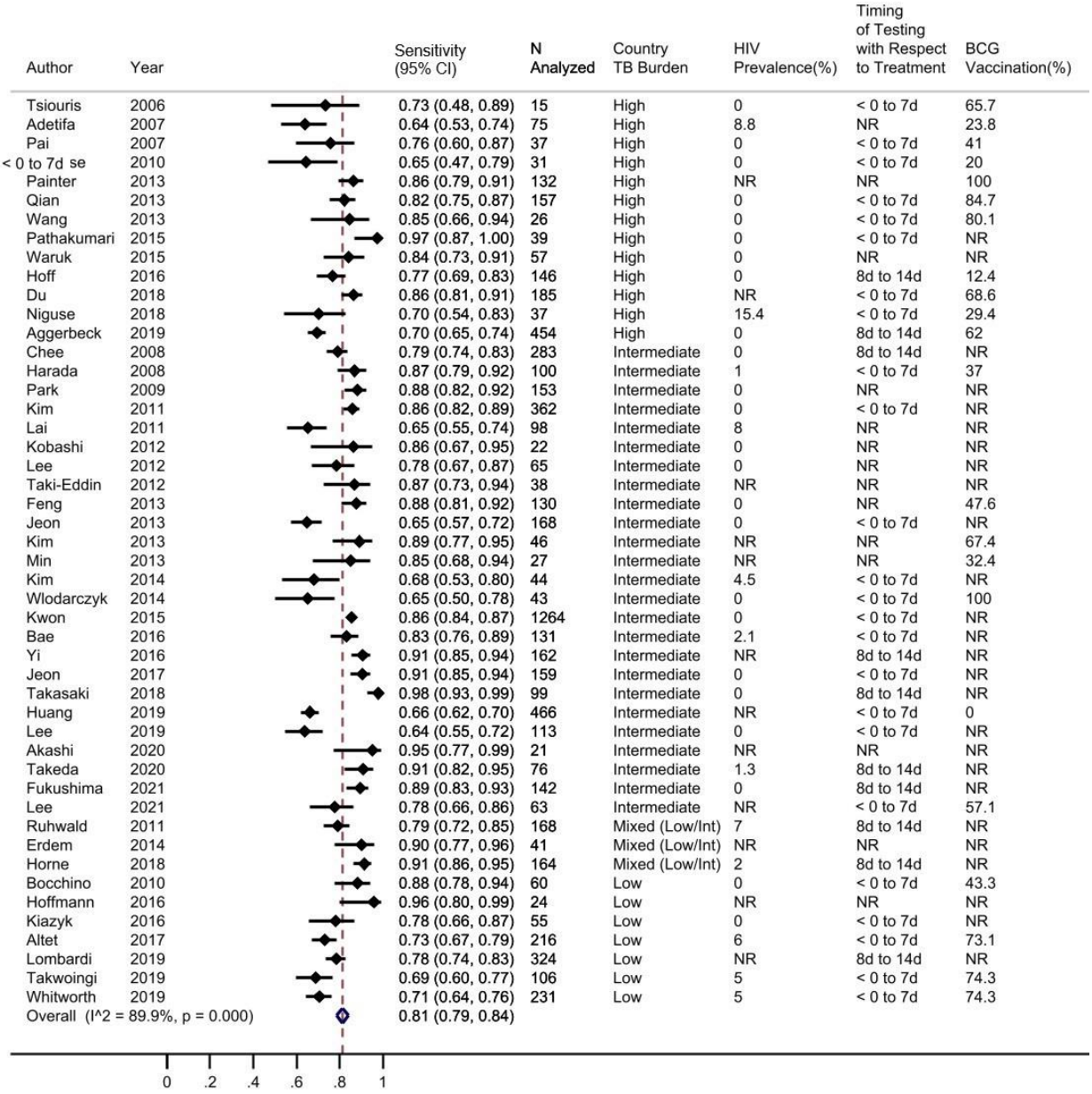
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TST=tuberculin skin test; TB=tuberculosis.

Figure 4. Individual Study and Pooled Estimates of Sensitivity for the T-SPOT.*TB* Test for TB Infection



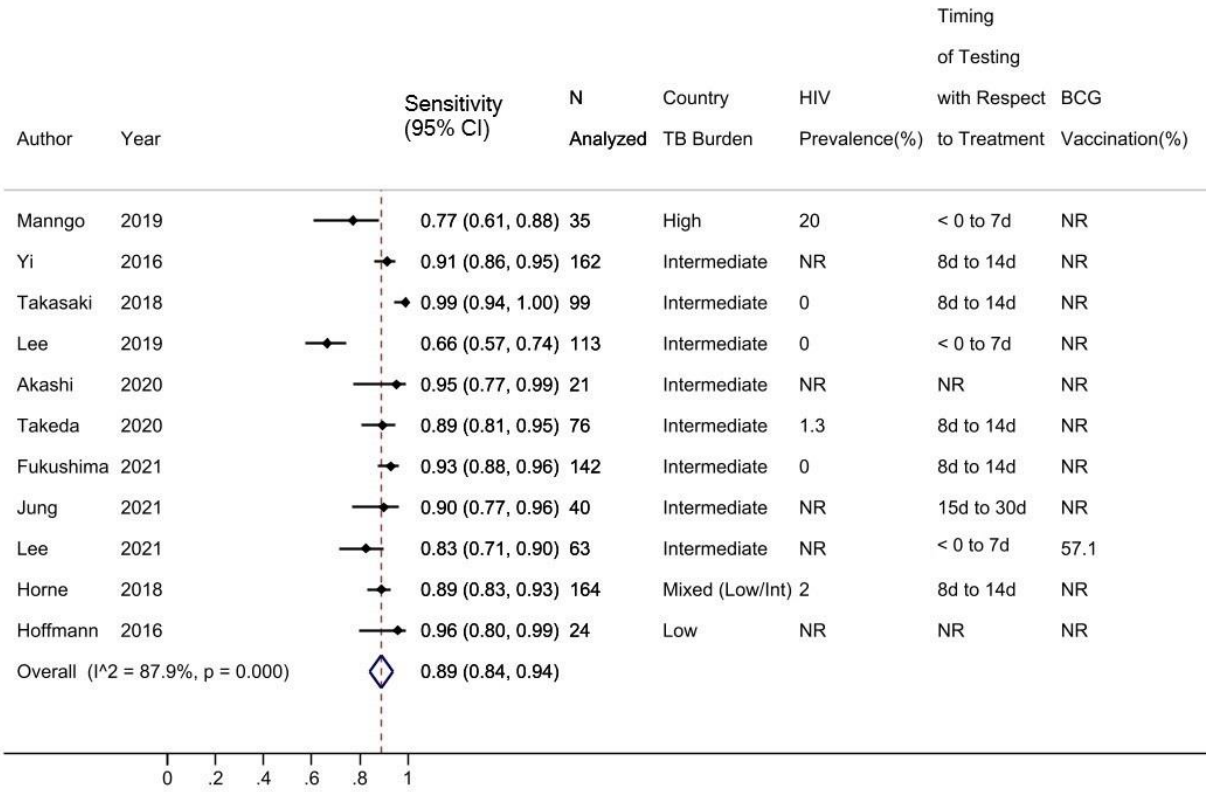
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; Int=Intermediate; N=number; NR=not reported; TB=tuberculosis.

Figure 5. Individual Study and Pooled Estimates of Sensitivity for the QFT-GIT Test for TB Infection



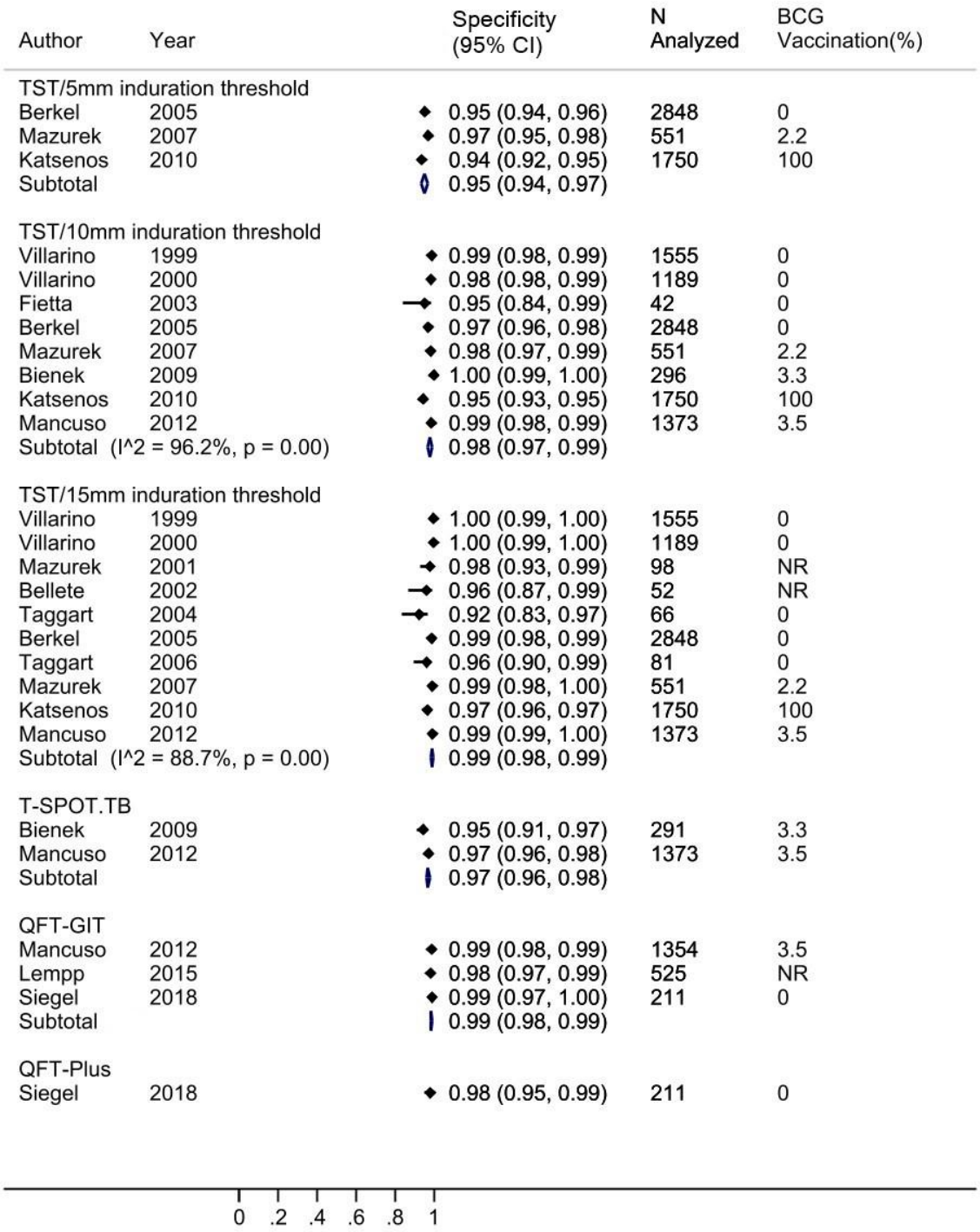
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis.

Figure 6. Individual Study and Pooled Estimates of Sensitivity for the QFT-Gold Plus Test for TB Infection



Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis.

Figure 7. Individual Study and Pooled Estimates of Specificity for Various Thresholds of the TST and IGRA Tests for TB Infection



Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; QFT-GIT=QuantiFERON-TB Gold-In-Tube® test (3rd-generation test); QFT-Plus=QuantiFERON-TB Gold Plus® test (4th generation test); T-SPOT.*TB*=Commercial ELISpot Assay; TST=tuberculin skin test.

Table 1. CDC (2020) Recommended LTBI Treatment Regimens

Priority*	Recommendation Strength†	Drug(s)	Duration	Dose	Frequency	Total Doses
Preferred	Strong	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‡	12
Preferred	Strong	RIF	4 months	10 mg/kg Maximum dose: 600 mg	Daily	120
Preferred	Conditional	INH and RIF	3 months	INH: 5 mg/kg rounded up to the nearest 50 or 100 mg; 300 mg maximum RIF: 10 mg/kg; 600 mg maximum	Daily	90
Alternative	Strong (HIV negative)	INH	9 months	5 mg/kg Maximum dose: 300 mg	Daily	270
	Conditional (HIV positive)			15 mg/kg Maximum dose: 900 mg	Twice weekly‡	76
Alternative	Conditional	INH	6 months	5 mg/kg Maximum dose: 300 mg	Daily	180
	Conditional			15 mg/kg Maximum dose: 900 mg	Twice weekly‡	52

Information is from CDC (2020) recommended regimens.[30]

**Preferred:* Excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative*: excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.

†Strong indicates benefits outweigh risks and evidence quality is at least moderate; conditional indicates it is uncertain whether benefits outweigh risks.

‡Intermittent regimens must be provided via directly observed therapy (i.e., healthcare worker observes the ingestion of medication).

Abbreviations: CDC=Centers for Disease Control and Prevention; HIV=human immunodeficiency virus; INH=isoniazid; LTBI=latent TB infection; RIF=rifampin; RPT=rifapentine.

Table 2. Summary of Sensitivity and Specificity Estimates for Various Thresholds of the TST and IGRA Tests

Test	Sensitivity Number of Studies (Total N)	Pooled Estimate (95% CI), I^2	Specificity Number of Studies (Total N)	Pooled Estimate (95% CI), I^2
TST (5-mm threshold)	12 (1,323)	0.80 (0.74 to 0.87), 94.2%	3 (5,149)	0.95 (0.94, 0.97), NA*
TST (10-mm threshold)	15 (1,427)	0.81 (0.76 to 0.87), 91.4%	8 (9,604)	0.98 (0.97 to 0.99), 96.2%
TST (15-mm threshold)	9 (1,004)	0.60 (0.46 to 0.74), 96.5%	10 (9,563)	0.99 (0.98 to 0.99), 88.7%
IGRA; T-SPOT.*TB*	37 (5,367)	0.90 (0.87 to 0.92), 93.2%	2 (1,664)	0.95 (0.91 to 0.97)† 0.97 (0.96 to 0.98)†
IGRA; QFT-GIT	48 (7,055)	0.81 (0.79 to 0.84), 89.9%	3 (2,090)	0.99 (0.98 to 0.99), NA*
IGRA; QFT-Plus	11 (939)	0.89 (0.84 to 0.94), 87.9%	1 (211)	0.98 (0.95 to 0.99)†

* I^2 was not calculated when fewer than four studies were available.
† Fewer than three studies were available, so we did not conduct a quantitative synthesis.

Abbreviations: CI=confidence interval; I^2=the proportion of variation in study estimates due to heterogeneity; IGRA=interferon-gamma release assay; mm=millimeter; N=number of patients; NA=not applicable; QFT-GIT=QuantiFERON-TB Gold-In-Tube® test (3rd-generation test); QFT-Plus=QuantiFERON-TB Gold Plus® test (4th generation test); T-SPOT.*TB*=Commercial ELISPOT Assay; TST=tuberculin skin test.

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 1. Benefits of screening	0, 0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ 2. Accuracy of screening TST 5-mm accuracy	Sn 12 (1,323) Sp 3 (5,149) Observational studies of test accuracy	Sn pooled 0.80 (95% CI, 0.74 to 0.87, I^2=94.2%) Sp pooled 0.95 (95% CI, 0.94 to 0.97)	Consistent but imprecise for Sn Consistent and precise for Sp	Fair to Good	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies Reporting bias not detected	Moderate for Sn High for Sp	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)
KQ 2. Accuracy of screening TST 10-mm accuracy	Sn 15 (1,427) Sp 8 (9,604) Observational studies of test accuracy	Sn pooled 0.81 (95% CI, 0.76 to 0.87, I^2=91.4%) Sp pooled 0.98 (95% CI, 0.97 to 0.99, I^2=96.2%)	Consistent but imprecise for Sn Consistent and precise for Sp	Fair to Good	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies Reporting bias not detected	Moderate for Sn High for Sp	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)

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening TST 15-mm accuracy (continued)	Sn 9 (1,004) Sp 10 (9,563) Observational studies of test accuracy	Sn pooled 0.60 (95% CI, 0.46 to 0.74, I^2=89.8%) Sp pooled 0.99 (95% CI, 0.98 to 0.99, I^2=88.7%)	Inconsistent and imprecise for Sn Consistent and precise for Sp	Fair to Good	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies Reporting bias not detected	Low for Sn High for Sp	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
KQ 2. Accuracy of screening TST reliability	Interrater reliability 3 (3,142) Observational studies of test accuracy	Kappa 0.69 and 0.79 in two 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	Fair	Reliability may be affected by the populations in which it is assessed; studies did not use similar methods for evaluating reliability Reporting bias not detected	Low	TST using Mantoux procedure with intermediate-strength dose of PPD TST administration and interpretation dependent on the use of appropriate, standardized technique

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening IGRA T-SPOT.*TB* accuracy (continued)	Sn 37 (5,367) Sp 2 (1,664) Observational studies of test accuracy	Sn pooled 0.90 (95% CI, 0.87 to 0.92; I^2=93.2%) Sp from 2 studies: 0.95 (0.91 to 0.97) 0.97 (0.96 to 0.98)	Consistent and precise for Sn and Sp	Fair to Good for Sn Fair for Sp	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies varied with respect to how they reported borderline results Reporting bias not detected	High for Sn Moderate for Sp	Lack of direct test for LTBI requires extrapolation of test characteristics from active TB (Sn) and healthy, low-risk (Sp) populations

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening IGRA T-SPOT.*TB* reliability (continued)	Interrater reliability 2 (404) Reproducibility 1 (130) Test-retest 2 (296) Observational studies of test accuracy	1 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) 1 study conducted among immigrants who were close contacts of active TB patients with 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%) 1 study enrolling HCWs: 9/111 (8.1%) tests changed from negative to positive and 10/19 (52.6%) changed from positive to negative at 2 weeks. 1 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	Fair	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies varied with respect to how they reported borderline results Reporting bias not detected	Low	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 on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening IGRA QFT-GIT accuracy (continued)	Sn 48 (7,055) Sp 3 (2,090) Observational studies of test accuracy	Sn pooled 0.81 (95% CI, 0.79 to 0.84, I^2=89.9%) Sp pooled 0.99 (95% CI, 0.98 to 0.99)	Consistent and precise for Sn and Sp	Fair to good for Sn Fair for SP	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies varied with respect to how they reported indeterminate results Reporting bias not detected	High for Sn Moderate for Sp	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 on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening IGRA QFT-GIT reliability (continued)	Interrater reliability 1 (146)	Across all 4 tests (2 samples from each participant analyzed by manual and automated ELISA): 88.6% were concordant (16.0% concordant positive and 72.6% concordant negative); 11.0% 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)	Consistency unknown for single study, precision unknown	Fair	High loss to followup between initial and followup testing Reporting bias not detected	Insufficient	QFT-GIT requires proper specimen handling prior to assay, range of subjects including healthy controls, active TB, and close contacts
	Reproducibility 1 (130)	Number of discordant results in participants who had 2 samples drawn simultaneously: 10 /172 (5.8%)	Consistency unknown for single study, precision unknown				
	Test-retest reliability 2 (296)	1 study enrolling HCWs, 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)	Inconsistent and imprecise for test-retest reliability				
	Interlaboratory reliability 1 (91) Observational studies of test accuracy	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, precision unknown				

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 2. Accuracy of screening IGRA QFT-Plus accuracy (continued)	Sn 11 (939) Sp 1 (211) Observational studies of test accuracy	Sn pooled 0.89 (95% CI, 0.84 to 0.94; I^2=87.9%) Sp from 1 study: 0.98 (95% CI, 0.95 to 0.99)	Consistent and precise for Sn Consistency unknown for single study, precise for Sp	Fair	Independent interpretation of test not reported Reporting bias not detected	Moderate for Sn Low for Sp	QFT-Plus requires proper specimen handling prior to assay
KQ 3. Benefits of treatment 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 with 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	Good (fair to good for sensi-tivity 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 Reporting bias not detected	High for benefit	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 INH groups vs. placebo	Imprecise, consistency unknown	Good	Small number of events	Low for benefit	Same as above for main analysis applicability
	1 RCT (27,830)*	All-cause mortality: NR by group	Imprecise, consistency unknown	Good	Data on all-cause mortality NR by group	Insufficient	Same as above for main analysis applicability
KQ 3. Benefits of treatment RIF vs. INH	2 RCTs (6,910)	Developing active TB: 8 vs. 9 All-cause mortality: 22 vs. 15	Imprecise, consistency unknown	Fair to good	Open label, but used fairly rigorous methods with masked review panel. Unclear allocation concealment.	Low for non-inferiority of shorter-duration RIF	Study population included those 18 years or older with a positive TST/IGRA. Second study required patients to be at increased risk of progression to active TB. About half of participants were ages 18–35 years.

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 3. Benefits of treatment RIF vs. INH (continued)	1 RCT (847)	Deaths due to TB: 0 vs. 0	Imprecise, consistency unknown	Good	No events. Unclear allocation concealment.	Insufficient	
KQ 3. Benefits of treatment RPT+INH vs. INH	1 RCT (6,886)‖	Developing active TB: 5 vs. 10¶	Consistency NA, single study; reasonably precise for developing active TB and all-cause mortality	Fair	Open label; single study, no data for deaths due to TB	Low for non-inferiority of RPT+INH	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
	1 RCT (263)	Deaths due to TB: 0 vs. 0	Consistency NA, single study; imprecise (no events)	Fair	Open label; small study. Noncompletion and consent withdrawal significantly higher in 9H group. No data for developing active TB.	Insufficient	Study completed in Taiwan; age ≥12 years, mean age 32; 58% male; all subjects had close contact with an active TB case and had positive TST within 1 month after exposure
	2 RCTs (7,149)	All-cause mortality: 30 vs. 34	Consistency NA, single study. Reasonably precise for all-cause mortality	Fair	Both studies were open label. One had higher noncompletion and consent withdrawal in 9H group.	Low for non-inferiority of RPT+INH	As above
KQ 4. Harms of screening	0, 0	No eligible studies	NA	NA	NA	Insufficient	NA

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 5. Harms of treatment 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 with placebo; NNH=279 *Sensitivity analysis:* Pooled RR: 5.04† (95% CI, 2.50 to 10.15; I 2=0%) Dose-response effect seen with increased risk with longer treatment duration	Consistency NA, single study in main analysis; consistent across studies in sensitivity analysis; imprecise	Fair	Harm ascertainment techniques not well described. Studies used in sensitivity analysis limited by ascertainment bias	Moderate for harm	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, single study; imprecise	Fair	Rare number of events Harm ascertainment techniques not well described	Low for harm	Same as above for hepatotoxicity
	1 RCT (27,830)* Sensitivity analysis with 4 RCTs (55,398)	Discontinuation of treatment due to adverse events: *Main analysis:* RR: 1.50† (95% CI, 1.18 to 1.89; NNH=167) *Sensitivity analysis:* Pooled RR: 1.58 (95% CI, 1.00 to 2.49)	Consistency NA, single study in main analysis; reasonably consistent across the studies in sensitivity analysis; reasonably precise.	Fair	Harm ascertainment techniques not well described Studies used in sensitivity analyses limited by lack of prespecification of harm outcomes, ascertainment bias	Moderate for harm	Same as above for hepatotoxicity
	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, single study; reasonably precise	Fair	GI harms not prespecified, ascertainment bias	Low for harm	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 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 5 INH vs. RIF	4 RCTs (7,390)	Hepatotoxicity: Pooled RR, 4.22 (95% CI, 2.21, 8.06), 3 trials, 7,339 participants Death from hepatotoxicity: No events reported in any arms of any study	Consistent; precise	Fair to good	3 trials were open label, 1 trial with high attrition	High for greater risk of hepatotoxicity with INH	Trials published in 2004, 2008, 2012, 2018[α]; participants had positive TST following Canadian guidelines or were inmates diagnosed with LTBI at jail entry
	4 RCTs (7,390)	Discontinued due to AEs: RR, 2.25 (95% CI, 0.90 to 5.59), 3 trials, 7,339 participants	Inconsistent; imprecise	Fair to good	3 trials were open label, 1 trial with high attrition	Low	Same as above
	3 RCTs (7,274)	GI intolerance: 20 vs. 19 The calculated RRs for the two trials with sufficient data were: 0.34 (95% CI, 0.03, 3.23) and 1.16 (95% CI, 0.62 to 2.19).	Inconsistent, imprecise	Fair	1 trial with high attrition; duration of followup may be inadequate; ascertainment bias	Insufficient	Same as above
KQ 5 RPT + INH vs. INH	2 RCTs (7,149)[‖]	Hepatotoxicity From PREVENT TB trial: grade 3 or 4: 210 vs. 219[¶], RR, 0.90 (95% CI, 0.75 to 1.08); hepatoxicity attributable to study drug: 17 vs. 97, RR, 0.16 (95% CI, 0.10, 0.28). From Sun, 2018: AST/ALT > 3x ULN normal: 6 vs. 13, RR, 0.46 (95% CI, 0.18, 1.17); clinically relevant hepatotoxicity: 2 vs. 7, RR, 0.28 (95% CI, 0.06, 1.34); mortality due to hepatotoxicity: 0 vs. 0	Consistent, imprecise	Fair	One study was open label; one had high overall attrition, and the other had higher withdrawal and noncompletion rates in one group	Low (favoring less hepatotoxicity with RPT+INH)	PREVENT TB 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; one study completed in Taiwan; all subjects had close contact with an active TB case and had positive TST within 1 month after exposure

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 5 RPT + INH vs. INH (continued)	2 RCTs (7,149)	Discontinuation due to AE: PREVENT TB: 186 vs. 136, RR, 1.28 (95% CI, 1.03 to 1.59) in Sun, 2018 12 vs. 7, RR, 1.70 (95% CI, 0.69, 4.19)	Consistent, precise	Fair	One study was open label; one had high overall attrition, and the other had higher withdrawal and noncompletion rates in one group	Moderate (favoring lower discontinuation due to AE with INH)	Same as above
	2 RCTs (7,149)	Systemic drug reactions and hypersensitivity PREVENT TB Possible hypersensitivity: 146 vs. 17; RR, 8.04 (95% CI, 4.88 to 13.26); any clinically significant systemic drug reaction: 138 vs. 15, RR, 8.7 (95% CI 5.1, 14.7). Sun, 2018: Any systemic drug reaction: 5 vs. 0, RR, 10.9 (95% CI, 0.6, 195.5)	Consistent, imprecise	Fair	One study was open label; one had high overall attrition, and the other had higher withdrawal and noncompletion rates in one group	Low (favoring fewer systemic drug reactions with INH)	Same as above
RIF + INH vs. RPT + INH	1 RCT (52)	Hepatotoxicity: 4 vs. 3 participants Mortality from hepatotoxicity: 0 vs. 0 Discontinuation due to AEs (hepatotoxicity): 1 vs. 0	Consistency NA, single study; imprecise	Fair	One small pilot trial with small sample size and very few events	Insufficient	Subjects ages 16 to 65 years with confirmed LTBI at clinics in London, UK; Mean age 32.5 vs. 38.2 years

Table 3. Summary of Evidence on Screening for LTBI in Adults

Key Question and Topic	No. of Studies (k), No. of Participants (n)	Summary of Findings	Consistency and Precision	Study Quality	Limitations (Including Reporting Bias)	Overall Strength of Evidence	Applicability
KQ 5 RPT + INH weekly vs. RPT + INH twice weekly	1 RCT (3,738)	Hepatotoxicity: 13 vs. 15 participants; RR, 0.88 (95% CI, 0.42, 1.84) Mortality from hepatotoxicity: 0 vs. 0 Discontinuation due to AE: 77 vs. 82; RR, 0.95 (95% CI, 0.70, 1.28) Hypersensitivity or allergy: 43 vs. 65; RR, 1.69 (95% CI, 1.26, 2.27) Flu-like symptoms: 46 vs. 29; RR, 1.60 (95% CI, 1.01, 2.54)	Consistency NA, single study; imprecise	Fair	Open label; study shortened treatment duration because of adverse effects	Insufficient	Subjects ages 50 to 69 years living in rural China with a positive QFT-GIT; 45% female

* 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).

† 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 five RCTs included in the sensitivity analysis ranged from 2 to 10 years; one study followed patients for 2 years, one for 5 years (IUAT), two for 7 years, and one for 10 years.

§ 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; ELISA=enzyme-linked immunosorbent assay; HCW=healthcare worker; HIV=human immunodeficiency virus; HH=household; I^2=the proportion of variation in study estimates due to heterogeneity; IGRA=interferon-gamma release assay; INH=isoniazid; IUAT=International Union Against Tuberculosis; k=number of studies; KQ=key question; LTBI=latent tuberculosis infection; n=number; NA=not applicable; NNT=number needed to treat; No.=number; NR=not reported; PPD=purified protein derivative; QFT-GIT=QuantiFERON-TB Gold-In-Tube® test (3rd-generation test); QFT-Plus=QuantiFERON-TB Gold Plus® test (4th generation test); RCT=randomized, controlled trial; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis; T-SPOT.*TB*=Commercial ELISPOT Assay; TST=tuberculin skin test; vs.=versus.

Appendix A Table 1. Screening Recommendations of Other Groups

Organization, Year	Screening Recommendation	Treatment Recommendation
ATS/IDSA/CDC, 2017[37]	A clinical practice guideline from the ATS, IDSA, and CDC recommends screening for LTBI to identify persons who may benefit from treatment before progression to active TB infection.	Not applicable
NTCA/CDC, 2019 or 2020	A committee convened by the NTCA and CDC recommended continuation of preplacement baseline LTBI testing using either IGRA or TST and symptom evaluation for all healthcare personnel with no prior documented history of LTBI or TB disease.[199]	A committee convened by the NTCA and CDC recommends short-course (3- to 4-month) rifamycin-based treatment regimens, which are preferred over longer-course (6- to 9-month) isoniazid monotherapy for treatment of LTBI.[40]
WHO, 2018[45]	The WHO recommends systematic testing and treatment for: • All persons living with HIV, • Patients initiating anti-TNF treatment • Patients receiving dialysis • Patients preparing for an organ or hematological transplant • Patients with silicosis • Persons residing in correctional facilities in countries with high TB incidence • Healthcare workers in countries with high TB incidence • Immigrants in countries with high TB incidence • Asymptomatic individuals of all ages in countries with a low TB incidence who are household contacts of persons with active TB. The WHO recommends either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) to test for LTBI.	The WHO recommends the following: Isoniazid monotherapy for 6 months is recommended for treatment of LTBI in both adults and children in countries with high and low TB incidence, rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for children and adolescents age <15 years in countries with a high TB incidence, and a combination of rifapentine and isoniazid weekly for 3 months may be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for both adults and children in countries with a high TB incidence.
NICE, 2019[200]	NICE recommends TST testing in adults and children ages 2 to 65 who are close contacts of a person with pulmonary or laryngeal TB. Children younger than 2 years and adults who are immunocompromised should be assessed for risk before being tested. Persons from underserved groups, including persons experiencing homelessness, persons who misuse substances, persons residing in correctional facilities, and vulnerable migrants, who are younger than 65 years should be offered IGRA testing.	NICE recommends 3 months of isoniazid (with pyridoxine) and rifampicin to persons younger than 35 years if hepatotoxicity is a concern after an assessment of both liver function (including transaminase levels) and risk factors and 6 months of isoniazid (with pyridoxine) if interactions with rifamycins are a concern, for example, in persons with HIV or who have had a transplant.
AAP/ACOG[197]	Current joint guidelines from the AAP and ACOG recommend screening for latent TB in early pregnancy for women at high risk for TB, including recent TB exposure, HIV infection, risk factors increasing risk of progression to active disease (such as diabetes, lupus, cancer, alcoholism, and drug addiction), use of immune-suppressing drugs such as TNF-alpha inhibitors or chronic steroids, renal failure on dialysis, homelessness, living or working in long-term care facilities such as nursing homes and prisons, being medically underserved, and being born in a country with high prevalence of TB.	

Appendix A Table 1. Screening Recommendations of Other Groups

Organization, Year	Screening Recommendation	Treatment Recommendation
CTS/CLA/PHAC[201]	The 7th Edition of the Canadian Tuberculosis Standards by the CTS, CLA, and PHAC recommends consideration of screening for the following groups: • Foreign-born persons • Persons with non-HIV immune suppression and other medical or behavioral risk factors for TB • Long-term visitors to countries with higher TB incidence • TB contacts • Persons with HIV infection • Canadian-born Aboriginal Peoples • Children • Employees and users of healthcare and correctional facilities	The 7th Edition of the Canadian Tuberculosis Standards by the CTS, CLA, and PHAC recommends self-administered isoniazid (INH) taken daily for 9 months (9INH) for the treatment of LTBI. Acceptable alternatives include daily self-administered INH for 6 months (6INH), and daily self-administered INH and rifampin (RMP) for 3–4 months.

Abbreviations: AAP=American Academy of Pediatrics; ACOG=American College of Obstetrics and Gynecology; ATS=American Thoracic Society; CDC=Centers for Disease Control and Prevention; CLA=Canadian Lung Association; CTS=Canadian Thoracic Society; HIV=human immunodeficiency virus; IDSA=Infectious Disease Society of America; IGRA=interferon-gamma release assays; INH=isoniazid; LTBI=latent tuberculosis infection; NICE=National Institute for Health and Care Excellence; NTCA=National Tuberculosis Controllers Association; PHAC=Public Health Agency of Canada; RIF=rifampin; RPT=rifapentine; TB=tuberculosis; TST=tuberculin skin tests; WHO=World Health Organization.

CQ 1. What risk assessment tools are available for use in primary care to identify adults to screen for LTBI? How do the tools incorporate race and ethnicity?

From the prior review, both the Task Force (TF) and the Evidence-based Practice Center (EPC) identified the need for tools to determine efficient ways of identifying candidates for LTBI screening and treatment. In current clinical practice, these tools are generally in the form of a checklist to help clinicians identify patients who should have further consideration for LTBI screening. The CDC recommends LTBI screening for persons at higher risk for being infected with TB bacteria, as well as those who are at higher risk of developing TB disease once infected with *Mycobacterium tuberculosis.*

The CDC provides an example risk assessment tool from the California Department of Public Health (CDPH).[35] The tool recommends screening for persons with any of the following three risk factors: temporary or permanent residence of 1 month or greater in a country with a high TB rate, current or planned immunosuppression, and close contact during lifetime with someone who had TB disease. Many State departments of public health have adopted the CDPH risk assessment tool[202] or reference the CDC guidance, for example, Michigan,[203] Washington,[204] Ohio,[205] Nevada,[206] and Pennsylvania.[207] The Wisconsin Department of Health Services has a similar risk assessment and symptom evaluation tool, and some health departments have adopted this tool.[208, 209] Other State public health departments have developed their own risk assessment tools, such as the Tennessee Department of Health and the Virginia Department of Health.[210,211,212] For example, the Virginia tool includes the risk factor categories that are in the CDPH tool as well as the following: birth, travel, or residence in a country with an elevated TB rate for at least 3 months and medical conditions increasing risk for progression to TB disease, including radiographic evidence of prior healed TB, low body weight (10% below ideal), silicosis, diabetes mellitus, chronic renal failure or on hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant, and head and neck cancer.[213]

The rationale for the risk factors included in the tools is largely based on LTBI disease prevalence data in various populations. For example, 71 percent of all cases of active TB in the United States in 2019 occurred among persons born outside the US.[6, 214] The top five countries contributing to these cases were Mexico, the Philippines, India, Vietnam, and China.[6, 214] Other populations are highlighted because of conditions that confer relative or actual immunosuppression. **Appendix A Table 2** summarizes data on LTBI prevalence in populations that are most often considered for LTBI screening. The data for the prevalence estimates in the table sometimes come from small cohorts.

We identified one prospective, cross-sectional study with 455 participants that evaluated a questionnaire to predict positive IGRA results in asymptomatic persons.[215] Participants ages 15 years or older from the United Arab Emirates were enrolled between August 2016 and May 2017 from hospital outpatient clinics for medical problems other than infection or TB assessment. Of those enrolled, 240 (53%) had an IGRA test performed. All enrollees completed a risk assessment questionnaire, which consisted of five questions assessing potential high-risk exposures (e.g., travel to high-TB-burden area, contact with persons with or suspected to have TB). In a multivariate logistic regression analysis, none of the risk assessment questions was associated with positive IGRA results.

None of the tools or studies we identified explicitly incorporated race or ethnicity.

Appendix A Table 2. Prevalence of Latent Tuberculosis Infection by High-Risk Category From Studies Published in English, French, or Spanish, 2009 Through 2014*

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)	Total Population Contributing to Effect Estimates (Number of Studies)
Persons residing in correctional facilities	45.5 (23.1–87.6)	NR	NR	2.6 (0.03–9.8)	5801 (2)† 331,773 (3)‡
Persons who lived in 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)	29,434 (2)§ 1,479,542,654 (1)‖
Persons who use illicit drugs	85.0 (0.3–86.7)	45.8 (34.1–57.5)	63.0 (1.4–66.4)	6.0¶	872 (1)#
Persons experiencing homelessness	45.6 (20.5–79.8)	NR	53.8 (18.6–75.9)	2.2 (0.1–4.3)	32,108 (1)** 338,568 (1)††

* Adapted from Getahun et al. (2015).[9] Data are from studies conducted in countries with a TB incidence of <1 per 1,000 population. We omitted estimates for populations that are not within the scope of this report (e.g., close contacts of active TB patients; 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, including persons living 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).

† All persons residing in correctional facilities were systematically screened for TB.

§ Based on reported annual or year-end census multiplied by number of years studied. Unclear if total incarcerations is equal to unique number of persons residing in correctional facilities.

‖ All newly immigrated persons were systematically screened for TB.

¶ Single study.

Cases identified by national TB registry. Denominator based on number of newly arrived immigrants over 7-year period.

g Mixed population of HIV-positive and -negative persons.

** Systematically screened all residents of local homeless shelters (n=32,108).

†† Identified cases from TB registry. Denominator based on estimated homelessness in 1998 multiplied by 12-year study period. Unclear if denominator represents unique homeless persons over this time period.

Abbreviations: HIV=human immunodeficiency virus; LTBI=latent tuberculosis infection; NR=not reported; QFT-GIT=QuantiFERON-TB® Gold In-Tube (3rd-generation test); TB=tuberculosis; TNF=tumor necrosis factor; T-SPOT.*TB*=commercial IGRA assay; TST=tuberculin skin test.

Appendix B1. Original Literature Search Strategies

PubMed 2/24/2021

Screening=844; 844 imported
Interventions=1,462; 1,339 imported
Diagnostic Accuracy of Tests=1,265; 450 imported

Search Number	Query	Filters	Results
1	"Tuberculosis"[Mesh] OR "Latent Tuberculosis"[Mesh] OR "Mycobacterium tuberculosis"[Mesh] OR "latent tuberculosis"[tiab] OR "latent TB" OR LTBI[tiab] OR Mtb[tiab]		219,039
2	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case control"[tw] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		10,876,893
3	#1 NOT #2		158,401
4	Adult[MeSH] OR Adult*[tw] OR "middle age"[tw] OR "middle aged"[tw]		8,063,660
5	#3 AND #4		45,456
6	"Adolescent"[Mesh] OR adolescen*[tw] OR boys[tw] OR "Child"[Mesh] OR child[tw] OR children*[tw] OR childhood[tw] OR girls[tw] OR pediatric*[tw] OR paediatric*[tw] OR teen[tw] OR teens[tw] OR teenage*[tw] OR youth[tw] OR youths[tw]		3,679,569
7	#3 NOT#6		129,161
8	#5 OR #7		142,915
9	#5 OR #7	English	73,785
10	"Systematic Review"[pt] OR ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "Systematic Reviews as Topic"[Mesh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Umbrella Review"[tiab]		361,409
11	#9 AND #10		1,062
12	"randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized [tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]		4,993,768
13	#9 AND #12		19,697
14	"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"		2,697,181
15	#9 AND #14		12,854
16	"Interferon-gamma Release Tests"[Mesh] OR "Tuberculin Test"[Mesh] OR IGRA OR Mantoux* OR QFT OR "QFT Gold In Tube" OR "QFT-Gold In Tube" OR "QFT-GIT" OR "QFT-Plus" OR QuantiFERON* OR "tuberculin skin test"[tiab] OR TST[tiab] OR "T-SPOT" OR "T-SPOT.TB"		22,327
17	#16 AND #11		134
18	#16 AND #13		1,749
19	#16 AND #15		1,746

Appendix B1. Original Literature Search Strategies

Search Number	Query	Filters	Results
20	#17 OR #18 OR #19		2,968
21	#20 AND (“2015/01/30”[Date - Publication] : “3000”[Date - Publication])		844
22	“Isoniazid”[Mesh] OR INH OR isoniazid OR “Rifampin”[Mesh] OR Rifampin OR “rifapentine”[Supplementary Concept] OR rifapentine OR rifampicin		50,536
23	#22 AND #11		173
24	#22 AND #13		5,047
25	#22 AND #15		1,851
26	#23 OR #24 OR #25		5,533
27	#26 AND (“2015/01/30”[Date - Publication] : “3000”[Date - Publication])		1,462
28	“Clinical Laboratory Techniques”[MeSH] OR “Comparative Study” [Publication Type] OR “Diagnostic Test Approval”[MeSH] OR “Diagnostic Tests, Routine”[MeSH] OR “False Negative Reactions”[MeSH] OR “False Positive Reactions”[MeSH] OR “Mass Screening”[MeSH] OR “Predictive Value of Tests”[Mesh] OR “Reproducibility of Results”[Mesh] OR “Risk Assessment”[MeSH] OR “ROC Curve”[Mesh] OR “Sensitivity and Specificity”[Mesh] OR accuracy[tw] OR “false negative”[tw] OR “false positive”[tw] OR “likelihood ratio”[tw] OR “predictive value”[tw] OR reproducib*[tw] OR ROC[tw] OR screen*[tiab] OR sensitivity[tw] OR specificity[tw] OR test*[tiab]		8,915,578
29	#9 AND #28		31,163
30	#29 AND #16		5,831
31	#30 AND (“2015/01/30”[Date - Publication] : “3000”[Date - Publication])		1,265

Cochrane Library, 2/24/2021

Screening=108; 93 imported
Interventions=301; 203 imported (300 saved, 1 was from Special Collections tab and not saved)
Diagnostic Accuracy of Tests=118; 20 imported

#1 [mh ”Tuberculosis”] OR [mh ”Latent Tuberculosis”] OR [mh ”Mycobacterium tuberculosis”] OR “latent tuberculosis”:ti,ab OR “latent TB” OR LTBI:ti,ab OR Mtb:ti,ab 2598
#2 address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR “case report” OR “case reports” OR “case series” OR “comment”:pt OR “comment on” OR congress:pt OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR “legal case”:pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR ([mh ”Animals”] NOT [mh ”Humans”]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae 64489
#3 #1 NOT #2 2440
#4 [mh Adult] OR Adult*:ti,ab,kw OR “middle age”:ti,ab,kw OR “middle aged”:ti,ab,kw 775799
#5 #3 AND #4 1567
#6 [mh adolescent] OR adolescen*:ti,ab,kw OR boys:ti,ab,kw OR [mh child] OR child:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR [mh infant] OR infant*:ti,ab,kw OR

pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage*:ti,ab,kw OR youth:ti,ab,kw OR youths:ti,ab,kw 277813
#7 #3 NOT #6 1601
#8 #5 OR #7 2198
#9 #8 with Cochrane Library publication date from Jan 2015 to Feb 2021 1039
#10 [mh ^"clinical trials as topic"] OR (controlled:ti,ab AND trial:ti,ab) OR "controlled clinical trial":pt OR [mh "drug therapy"] OR "randomized controlled trial":pt OR "randomized controlled trial as topic":pt OR "single-blind method":pt OR "double-blind method":pt OR "random allocation":pt OR placebo:ti,ab OR randomized:ti,ab OR randomly:ti,ab OR trial:ti 1244856
#11 #9 AND #10 819
#12 [mh "Cohort Studies"] OR [mh "Epidemiologic Studies"] OR [mh " Follow-Up Studies"] OR [mh "Seroepidemiologic Studies"] OR "Evaluation Studies":pt OR [mh "Program Evaluation"] OR "observational study" OR "observational studies" 172800
#13 #9 AND #12 131
#14 [mh "Interferon-gamma Release Tests"] OR [mh "Tuberculin Test"] OR IGRA OR Mantoux* OR QFT* OR "QFT Gold In Tube" OR "QFT-Gold In Tube" OR "QFT-GIT" OR "QFT-Plus" OR QuantiFERON OR "QuantiFERON-Plus" OR "QuantiFERON-TB Gold Plus" OR "tuberculin skin test":ti,ab OR TST:ti,ab OR "T-SPOT" OR "T-SPOT.TB" 1520
#15 #14 AND #11 106
#16 #14 AND #13 18
#17 #15 OR #16 108
#18 [mh "Isoniazid"] OR INH OR isoniazid OR [mh "Rifampin"] OR Rifampin OR rifapentine OR rifampicin 3695
#19 #18 AND #11 299
#20 #18 AND #13 43
#21 #19 OR #20 301
#22 [mh "Clinical Laboratory Techniques"] OR "Comparative Study":pt OR [mh " Diagnostic Test Approval"] OR [mh "Diagnostic Tests, Routine"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR [mh "Mass Screening"] OR [mh "Predictive Value of Tests"] OR [mh "Risk Assessment"] OR [mh "ROC Curve"] OR [mh "Reproducibility of Results"] OR [mh "Sensitivity and Specificity"] OR accuracy:ti,ab,kw OR "false negative":ti,ab,kw OR "false positive":ti,ab,kw OR "likelihood ratio":ti,ab,kw OR "predictive value":ti,ab,kw OR ROC:ti,ab,kw OR reproducib*:ti,ab,kw OR screen*:ti,ab OR sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR test*:ti,ab 585814
#23 #9 AND #22 586
#24 #23 AND #14 118

Grey Literature
ClinicalTrials.gov, 8/4/2020
Screening (38 studies)
Condition box:

("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "glucose tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "Glucose Intolerance"

OR “glucose intolerance” OR “Prediabetic State” OR “prediabetic state” OR prediabet* OR “pre diabetes” OR “diabetes mellitus type 2” OR “type 2 diabetes mellitus”)
AND
Other terms box:
(“blood glucose” OR OGTT OR “glucose tolerance test” OR “Glycated Hemoglobin A” OR “hemoglobin A1c” OR HbA1c OR “fasting plasma glucose” OR “HbA(1c)” OR HbA1 OR HbA1c OR “HbA 1c” OR “glycosylated hemoglobin” OR “glycated hemoglobin” OR “oral glucose tolerance”) AND (screen* OR screening)
Used child limits Age Group Child (birth-17)
Put together in Expert search:
(“blood glucose” OR OGTT OR “glucose tolerance test” OR “Glycated Hemoglobin A” OR “hemoglobin A1c” OR HbA1c OR “fasting plasma glucose” OR “HbA(1c)” OR HbA1 OR HbA1c OR “HbA 1c” OR “glycosylated hemoglobin” OR “glycated hemoglobin” OR “oral glucose tolerance”) AND (screen* OR screening) AND AREA[ConditionSearch] (“Diabetes Mellitus, Type 2” OR “Glucose Tolerance” OR “glucose tolerance” OR “impaired glucose tolerance” OR IGT OR “impaired fasting glucose” OR IFG OR “Glucose Intolerance” OR “glucose intolerance” OR “Prediabetic State” OR “prediabetic state” OR prediabet* OR “pre diabetes” OR “diabetes mellitus type 2” OR “type 2 diabetes mellitus”) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] “Child”
38 studies, saved

Interventions

Pharmacological Interventions (123 studies):
Condition box:
(“Diabetes Mellitus, Type 2” OR “Glucose Tolerance” OR “glucose tolerance” OR “impaired glucose tolerance” OR IGT OR “impaired fasting glucose” OR IFG OR “glucose Intolerance” OR “glucose intolerance” OR “Prediabetic State” OR “prediabetic state” OR prediabet* OR “pre diabetes” OR “diabetes mellitus type 2” OR “type 2 diabetes mellitus”)
AND
Intervention/treatment box:
Actos OR Albiglutide OR Amaryl OR Biguanides OR Bydureon OR Byetta OR DiaBeta OR “Dipeptidyl-Peptidase IV Inhibitors” OR “Dipeptidyl peptidase IV inhibitor” OR dulaglutide OR Exenatide OR Fortamet OR Gliclazide OR glimepiride OR Glipizide OR “GLP-1 receptor agonist” OR “GLP-1 receptor agonists” OR “Glucagon-like peptide-1 receptor agonist” OR “Glucagon-like peptide-1 receptor agonists” OR Glucophage OR Glucotrol OR Glumetza OR Glyburide OR “Glynase PresTab” OR Linagliptin OR Liraglutide OR lixisenatide OR Lyxumia OR Meglitinides OR Metformin OR Micronase OR Ozempic OR Pioglitazone OR Prandin OR Repaglinide OR Rosiglitazone OR Saxagliptin OR semaglutide OR Sitagliptin OR “Sulfonylurea Compounds” OR Starlix OR Sulfonylureas OR Tanzeum OR Thiazolidinediones OR Tolazamide OR Tolbutamide OR Trulicity OR TZDs OR Victoza OR vildagliptin

Used Child Limits Age Group Child (Birth–17)
In Expert search:
AREA[ConditionSearch] (“Diabetes Mellitus, Type 2” OR “Glucose Tolerance” OR “glucose tolerance” OR “impaired glucose tolerance” OR IGT OR “impaired fasting glucose” OR IFG OR “glucose Intolerance” OR “glucose intolerance” OR “Prediabetic State” OR “prediabetic state”

OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus") AND AREA[InterventionSearch] (Actos OR Albiglutide OR Amaryl OR Biguanides OR Bydureon OR Byetta OR DiaBeta OR "Dipeptidyl-Peptidase IV Inhibitors" OR "Dipeptidyl peptidase IV inhibitor" OR dulaglutide OR Exenatide OR Fortamet OR Gliclazide OR glimepiride OR Glipizide OR "GLP-1 receptor agonist" OR "GLP-1 receptor agonists" OR "Glucagon-like peptide-1 receptor agonist" OR "Glucagon-like peptide-1 receptor agonists" OR Glucophage OR Glucotrol OR Glumetza OR Glyburide OR "Glynase PresTab" OR Linagliptin OR Liraglutide OR lixisenatide OR Lyxumia OR Meglitinides OR Metformin OR Micronase OR Ozempic OR Pioglitazone OR Prandin OR Repaglinide OR Rosiglitazone OR Saxagliptin OR semaglutide OR Sitagliptin OR "Sulfonylurea Compounds" OR Starlix OR Sulfonylureas OR Tanzeum OR Thiazolidinediones OR Tolazamide OR Tolbutamide OR Trulicity OR TZDs OR Victoza OR vildagliptin) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child" **123** studies saved

Separate Search for Nonpharmacological Interventions (177 studies):
Condition box:
("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "glucose tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "glucose intolerance" OR "Prediabetic State" OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus")
AND
Non-Pharmacological Interventions in Treatment/Interventions box:
(advice OR "Behavior Therapy" OR (behavior* AND therap*) OR (behavior* AND chang*) OR (behavior* AND modification*) OR "Caloric Restriction" OR ((child* AND parent*) and therap*) OR counsel* OR "cognitive behavior" OR "cognitive behavioral" OR "cognitive therap*" OR CBT OR "Diabetes Prevention Program" OR "Diabetes Prevention Programme" OR DPP OR ("Diabetes Prevention" AND (program* OR stud* OR trial*)) OR diet OR dietary OR Exercise OR "family intervention*" OR "family therap*" OR "Feedback, Psychological" OR "group therap*" OR "Health Behavior" OR "health behaviors" OR "health behavioral" OR "health behaviours" OR "health behaviour" OR "Health Education" OR "Health Education as Topic" OR "health education" OR "Health Promotion" OR "health promotion" OR "Life Style" OR lifestyle OR "life style" OR "Lifestyle Intervention" OR "Motivational Interviewing" OR "motivational interviewing" OR "non pharmacologic intervention" OR "nonpharmacologic intervention" OR "parent* intervention*" OR "patient education" OR "physical activity" OR "physically active" OR "psychological feedback" OR "Risk Reduction Behavior" OR "Risk Reduction Behavior" OR "Weight Loss" OR "Weight Reduction Programs")

Used Child Limits Age Group Child (Birth–17)
In Expert Search:
AREA[ConditionSearch] (EXPAND[Concept] "Diabetes Mellitus, Type 2" OR EXPAND[Concept] "Glucose Tolerance" OR EXPAND[Concept] "glucose tolerance" OR EXPAND[Concept] "impaired glucose tolerance" OR IGT OR EXPAND[Concept] "impaired fasting glucose" OR IFG OR EXPAND[Concept] "glucose Intolerance" OR EXPAND[Concept] "glucose intolerance" OR EXPAND[Concept] "Prediabetic State" OR EXPAND[Concept] "prediabetic state" OR prediabet* OR EXPAND[Concept] "pre diabetes" OR EXPAND[Concept] "diabetes mellitus type 2" OR EXPAND[Concept] "type 2 diabetes

mellitus") AND AREA[InterventionSearch] (advice OR "Behavior Therapy" OR (behavior* AND therap*) OR (behavior* AND chang*) OR (behavior* AND modification*) OR "Caloric Restriction" OR ((child* AND parent*) and therap*) OR counsel* OR "cognitive behavior" OR "cognitive behavioral" OR "cognitive therap*" OR CBT OR "Diabetes Prevention Program" OR "Diabetes Prevention Programme" OR DPP OR ("Diabetes Prevention" AND (program* OR stud* OR trial*)) OR diet OR dietary OR Exercise OR "family intervention*" OR "family therap*" OR "Feedback, Psychological" OR "group therap*" OR "Health Behavior" OR "health behaviors" OR "health behavioral" OR "health behaviours" OR "health behaviour" OR "Health Education" OR "Health Education as Topic" OR "health education" OR "Health Promotion" OR "health promotion" OR "Life Style" OR lifestyle OR "life style" OR "Lifestyle Intervention" OR "Motivational Interviewing" OR "motivational interviewing" OR "non pharmacologic intervention" OR "nonpharmacologic intervention" OR "parent* intervention*" OR "patient education" OR "physical activity" OR "physically active" OR "psychological feedback" OR "Risk Reduction Behavior" OR "Risk Reduction Behavior" OR "Weight Loss" OR "Weight Reduction Programs") AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"
177 studies saved

ClinicalTrials.gov Addendum, 8/21/2020

211 studies, **138** imported, and 73 duplicates discarded
Condition box:
("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "glucose tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "glucose intolerance" OR "Prediabetic State" OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus" NOT ("type 1 diabetes" OR "diabetes mellitus type 1"))
AND
Intervention/treatment box:
("hypoglycemic agent*" OR insulin)
Used child limits Age Group Child (birth-17)
In Expert search:
AREA[ConditionSearch] ("Diabetes Mellitus, Type 2" OR "Glucose Tolerance" OR "glucose tolerance" OR "impaired glucose tolerance" OR IGT OR "impaired fasting glucose" OR IFG OR "glucose Intolerance" OR "glucose intolerance" OR "Prediabetic State" OR "prediabetic state" OR prediabet* OR "pre diabetes" OR "diabetes mellitus type 2" OR "type 2 diabetes mellitus" NOT ("type 1 diabetes" OR "diabetes mellitus type 1")) AND AREA[InterventionSearch] (EXPAND[Concept] "hypoglycemic agent*" OR insulin) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] "Child"

Update Searches

PubMed, 12/3/2021
Screening = 178; **178** imported
Interventions = 429; **403** imported
Diagnostic Accuracy of Tests = 279; **111** imported

Appendix B1. Original Literature Search Strategies

Search number	Query	Filters	Results
1	"Tuberculosis"[Mesh] OR "Latent Tuberculosis"[Mesh] OR "Mycobacterium tuberculosis"[Mesh] OR "latent tuberculosis"[tiab] OR "latent TB" OR LTBI[tiab] OR Mtb[tiab]		224,533
2	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case control"[tw] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae		11,221,120
3	#1 NOT #2		162,172
4	Adult[MeSH] OR Adult*[tw] OR "middle age"[tw] OR "middle aged"[tw]		8,360,564
5	#3 AND #4		46,628
6	"Adolescent"[Mesh] OR adolescen*[tw] OR boys[tw] OR "Child"[Mesh] OR child[tw] OR children*[tw] OR childhood[tw] OR girls[tw] OR pediatric*[tw] OR paediatric*[tw] OR teen[tw] OR teens[tw] OR teenage*[tw] OR youth[tw] OR youths[tw]		3,809,282
7	#3 NOT #6		128,908
8	#5 OR #7		149,538
9	#5 OR #7	English	82,179
10	"Systematic Review"[pt] OR ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "Systematic Reviews as Topic"[Mesh] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab] OR "Umbrella Review"[tiab]		404,951

11	#9 AND #10		1,467
12	"randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized [tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]		5,265,701
13	#9 AND #12		22,173
14	"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"		2,920,425
15	#9 AND #14		13,901
16	"Interferon-gamma Release Tests"[Mesh] OR "Tuberculin Test"[Mesh] OR IGRA OR Mantoux* OR QFT OR "QFT Gold In Tube" OR "QFT-Gold In Tube" OR "QFT-GIT" OR "QFT-Plus" OR QuantiFERON* OR "tuberculin skin test"[tiab] OR TST[tiab] OR "T-SPOT" OR "T-SPOT.TB"		23,021
17	#16 AND #11		168
18	#16 AND #13		1,747
19	#16 AND #15		1,729
20	#17 OR #18 OR #19		2,948
21	#20 AND ("2020/08/24"[Date - Publication] : "3000"[Date - Publication])		178
22	"Isoniazid"[Mesh] OR INH OR isoniazid OR "Rifampin"[Mesh] OR Rifampin OR "rifapentine"[Supplementary Concept] OR rifapentine OR rifampicin		51,876
23	#22 AND #11		247
24	#22 AND #13		5,782
25	#22 AND #15		2,137
26	#23 OR #24 OR #25		6,365
27	#26 AND ("2020/08/24"[Date - Publication] : "3000"[Date - Publication])		429
28	"Clinical Laboratory Techniques"[MeSH] OR "Comparative Study" [Publication Type] OR "Diagnostic Test Approval"[MeSH] OR "Diagnostic Tests, Routine"[MeSH] OR "False Negative Reactions"[MeSH] OR "False Positive Reactions"[MeSH] OR "Mass Screening"[MeSH] OR "Predictive Value of Tests"[Mesh] OR "Reproducibility of Results"[Mesh] OR "Risk		9,275,529

	Assessment"[MeSH] OR "ROC Curve"[Mesh] OR "Sensitivity and Specificity"[Mesh] OR accuracy[tw] OR "false negative"[tw] OR "false positive"[tw] OR "likelihood ratio"[tw] OR "predictive value"[tw] OR reproducib*[tw] OR ROC[tw] OR screen*[tiab] OR sensitivity[tw] OR specificity[tw] OR test*[tiab]		
29	#9 AND #28		35,964
30	#29 AND #16		5,606
31	#30 AND ("2020/08/24"[Date - Publication] : "3000"[Date - Publication])		279

Cochrane Library
12/3/2021
Screening = 21; 17 imported
Interventions = 55; 37 imported
Diagnostic Accuracy of Tests = 22; 2 imported

#1 [mh "Tuberculosis"] OR [mh "Latent Tuberculosis"] OR [mh "Mycobacterium tuberculosis"] OR "latent tuberculosis":ti,ab OR "latent TB" OR LTBI:ti,ab OR Mtb:ti,ab2779
#2 address:pt OR “autobiography”:pt OR “bibliography”:pt OR “biography”:pt OR “case control” OR "case report" OR “case reports” OR “case series” OR “comment”:pt OR "comment on" OR congress:pt OR “dictionary”:pt OR “directory”:pt OR “editorial”:pt OR “festschrift”:pt OR “historical article”:pt OR “interview”:pt OR lecture:pt OR "legal case":pt OR “legislation”:pt OR letter:pt OR “news”:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR ([mh "Animals"] NOT [mh "Humans"]) OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae 69319
#3 #1 NOT #2 2607
#4 [mh Adult] OR Adult*:ti,ab,kw OR "middle age":ti,ab,kw OR "middle aged":ti,ab,kw 833674
#5 #3 AND #4 1672
#6 [mh adolescent] OR adolescen*:ti,ab,kw OR boys:ti,ab,kw OR [mh child] OR child:ti,ab,kw OR children:ti,ab,kw OR girls:ti,ab,kw OR [mh infant] OR infant*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR teen:ti,ab,kw OR teens:ti,ab,kw OR teenage*:ti,ab,kw OR youth:ti,ab,kw OR youths:ti,ab,kw 293842
#7 #3 NOT #6 1734
#8 #5 OR #7 2351
#9 #8 with Cochrane Library publication date from Aug 2020 to Dec 2021 195
#10 [mh ^"clinical trials as topic"] OR (controlled:ti,ab AND trial:ti,ab) OR "controlled clinical trial":pt OR [mh "drug therapy"] OR "randomized controlled trial":pt OR "randomized controlled trial as topic":pt OR "single-blind method":pt OR "double-blind method":pt OR "random allocation":pt OR placebo:ti,ab OR randomized:ti,ab OR randomly:ti,ab OR trial:ti 1328622
#11 #9 AND #10 161

#12 [mh "Cohort Studies"] OR [mh "Epidemiologic Studies"] OR [mh " Follow-Up Studies"] OR [mh "Seroepidemiologic Studies"] OR "Evaluation Studies":pt OR [mh "Program Evaluation"] OR "observational study" OR "observational studies" 182368
#13 #9 AND #12 16
#14 [mh "Interferon-gamma Release Tests"] OR [mh "Tuberculin Test"] OR IGRA OR Mantoux* OR QFT* OR "QFT Gold In Tube" OR "QFT-Gold In Tube" OR "QFT-GIT" OR "QFT-Plus" OR QuantiFERON OR "QuantiFERON-Plus" OR "QuantiFERON-TB Gold Plus" OR "tuberculin skin test":ti,ab OR TST:ti,ab OR "T-SPOT" OR "T-SPOT.TB" 1657
#15 #14 AND #11 21
#16 #14 AND #13 2
#17 #15 OR #16 21
#18 [mh "Isoniazid"] OR INH OR isoniazid OR [mh "Rifampin"] OR Rifampin OR rifapentine OR rifampicin 3874
#19 #18 AND #11 55
#20 #18 AND #13 5
#21 #19 OR #20 55
#22 [mh "Clinical Laboratory Techniques"] OR "Comparative Study":pt OR [mh " Diagnostic Test Approval"] OR [mh "Diagnostic Tests, Routine"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR [mh "Mass Screening"] OR [mh "Predictive Value of Tests"] OR [mh "Risk Assessment"] OR [mh "ROC Curve"] OR [mh "Reproducibility of Results"] OR [mh "Sensitivity and Specificity"] OR accuracy:ti,ab,kw OR "false negative":ti,ab,kw OR "false positive":ti,ab,kw OR "likelihood ratio":ti,ab,kw OR "predictive value":ti,ab,kw OR ROC:ti,ab,kw OR reproducib*:ti,ab,kw OR screen*:ti,ab OR sensitivity:ti,ab,kw OR specificity:ti,ab,kw OR test*:ti,ab 623231
#23 #9 AND #22 109
#24 #23 AND #14 22

Gray Literature Searches

72 total in EndNote
ClinicalTrials.gov, 12/3/2021

Advanced search
Condition or disease box: "Latent Tuberculosis" OR "Mycobacterium tuberculosis" OR "latent TB" OR LTBI OR Mtb

Eligibility Criteria, Age Group: Selected checkboxes: Adult (18-64), Older Adult (65+)

Last Update Posted: From 02/24/2021 to 12/3/2021

65 results

Saved to EndNote using Irma Klering's modified ClinicalTrials.gov "Abs" filter to include more fields

WHO ICTRP, 2/24/2021
Advanced search

Condition box: "latent tuberculosis" OR “latent TB” or LTBI

Date of registration: 02/24/2021 to 12/3/2021

Recruitment status: All

7 results

Appendix B2. Eligibility Criteria

Criteria		Included	Excluded
Populations		**All KQs:** A priori specific populations of interest include those defined by age, sex, race/ethnicity, pregnancy, and higher risk for developing TB.* For each KQ, we looked for evidence to inform whether results differ by subgroups. **KQs 1, 4:** Asymptomatic adults belonging to populations at increased risk for LTBI.* Studies that combine eligible and ineligible populations were eligible if results were stratified for the eligible portion of the study population or the ineligible portion did not exceed 25% of the study population. **KQ 2:** For sensitivity outcome: Patients with bacteriologically confirmed active TB who have not yet received treatment or who had received no more than a few weeks of treatment. For specificity outcome: Healthy persons with no history of TB exposure or risks. Studies that combine children and adults or studies with both HIV-negative and HIV-positive persons (sensitivity outcome only) were eligible if results were stratified for the eligible portion of the study population or the ineligible portion did not exceed 25% of the study population. **KQs 3, 5:** Asymptomatic adults with confirmed LTBI (e.g., with a positive TST and without symptoms or chest X-ray findings indicative of active TB disease); otherwise, same criteria as for KQ 1 except that close contacts of active TB patients were eligible if LTBI was confirmed.	**KQs 1, 4:** 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 (often by specialty care providers). This includes persons 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. **KQ 2:** For sensitivity outcome: Persons with TB infection not confirmed by culture, AFB smear, or molecular tests. For specificity outcome: Persons with known history of TB or TB exposure, persons with HIV, and acutely ill persons.

Appendix B2. Eligibility Criteria

Criteria		Included	Excluded
Intervention and comparator		**KQs 1, 4:** Screening with TST, IGRA, or both compared with no screening. **KQs 2, 4:** TST using Mantoux method with intermediate strength dose of PPD and standard thresholds for positive test (i.e., 5 mm, 10 mm, and 15 mm based on risk factors for the persons being tested). Commercially available, FDA-approved IGRA tests: T-SPOT.*TB*, QFT-Gold in tube (QFT-GIT 3rd generation), and QFT-Gold Plus (4th generation). **KQs 3, 5:** Treatment with CDC-recommended regimen (INH daily for 6 or 9 months, INH twice weekly by directly observed therapy for 6 or 9 months, RIF daily for 4 months, or INH plus RPT weekly by directly observed therapy for 3 months) compared with placebo, no treatment, delayed treatment, or another eligible treatment.	**KQs 1, 4:** Studies with no comparator group. **KQs 2, 4:** Other tests, such as nucleic acid amplification and two-step TST. **KQs 3, 5:** Studies comparing other treatments or combinations (i.e., regimens that are not recommended by the CDC).
Outcomes		**KQs 1, 3:** Active TB disease, TB transmission, quality of life, and mortality (disease specific and overall). **KQ 2:** Sensitivity, specificity, and reliability (i.e., test-retest). **KQ 4:** False-positive test results leading to unnecessary testing or treatment, labeling, stigma, anxiety, and cellulitis. **KQ 5:** Hepatotoxicity, mortality from hepatotoxicity, nausea, vomiting, peripheral neuropathy, development of drug-resistant TB, and other specific adverse effects of medications.	**KQ 2:** Concordance rates among tests and other outcomes.

Appendix B2. Eligibility Criteria

Criteria		Included	Excluded
Study designs		**KQ 1:** RCTs and prospective cohort studies. **KQ 2:** RCTs, cohort studies, and cross-sectional studies. **KQ 3:** Systematic reviews and meta-analyses (including network meta-analyses)† and RCTs. **KQ 4:** Systematic reviews, RCTs, and prospective cohort studies. **KQ 5:** Systematic reviews and meta-analyses (including network meta-analyses), RCTs, prospective cohort studies, and case-control studies.	All other study designs not already indicated.
Setting		**KQ 1:** Study settings considered to be applicable to primary care, including primary care practices, homeless shelters, correctional facilities, college health settings, long-term care facilities, and public health clinics. **KQ 2:** Any setting. **KQs 3, 5:** Same as KQ 1, except that workplace settings are also eligible. **KQ 4:** Studies eligible for KQ 1 or 2.	**KQ 1:** HIV and subspecialty care settings and workplace settings that screen for LTBI as part of a formal surveillance program for occupational exposure. **KQs 3, 5:** Same as KQ 1, except that workplace settings are eligible.
Country		**KQs 1, 3, 5:** Countries categorized as "High" or "Very High" using the Human Development Index, as defined by the United Nations Development Programme. **KQ 2:** For sensitivity outcome: Studies in any country. For specificity outcome: Studies in low-TB-burden countries. **KQ 4:** Studies eligible for KQ 1 or 2.	**KQs 1, 3, 5:** Countries not categorized as "High" or "Very High" on the Human Development Index, as defined by the United Nations Development Programme. **KQ 2:** For specificity outcome: Studies in high-TB-burden countries.‡
Quality		Studies rated good or fair quality.	Studies rated poor quality.
Language		Full text published in English.	Not English language.

* Adult population subgroups at increased risk for developing active TB include 1) persons who have immigrated from TB-endemic countries; 2) persons who work or reside in facilities or institutions with high-risk individuals, such as homeless shelters, correctional facilities, nursing homes, and residential facilities; and 3) persons with increased risk for progression from LTBI to active TB because of underlying illness or use of medications, injection drug use, or radiographic evidence of prior healed TB.[216]

† We focused on the best evidence to address this KQ on treatment, focusing on the most recent high-quality meta-analysis rather than re-reviewing and synthesizing the primary RCTs that were summarized in the prior review on this topic (e.g., those comparing INH vs. placebo that were published in the 1960s and 1970s).

‡ High-TB-burden countries include the following: Angola, Bangladesh, Brazil, Cambodia, Central African Republic, China, Congo, the Democratic Republic of the Congo, Democratic People's Republic of Korea, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Peru, the Philippines, the Russian

Federation, Somalia, South Africa, Thailand, 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).[47]

Abbreviations: AFB=acid fast bacilli; CDC=Centers for Disease Control and Prevention; FDA=Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; INH=isoniazid; KQ=key question; LTBI=latent tuberculosis infection; PPD=purified protein derivative; QFT=QuantiFERON; QFT-GIT=QuantiFERON-TB Gold-In-Tube® test (3rd-generation test); RCT=randomized, controlled trial; RIF=rifampin; RPT=rifapentine; TB=tuberculosis; TNF-α=tumor necrosis factor-α; T-SPOT.*TB*=commercial IGRA assay; TST=tuberculin skin test; vs.=versus.

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Randomized, Controlled Trials and Cohort Studies

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 that are 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. In addition, intention-to-treat analysis is used for RCTs.
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. Intention-to-treat analysis is lacking for RCTs.
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. Intention-to-treat analysis is lacking for RCTs.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[48]

Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, and adequately described
- Credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Indeterminate results handled in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Reliable screening test

Definition of Ratings Based on Above Criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; assesses reliability of test; has few or handles indeterminate results in a reasonable manner; includes large number (greater than 100) of broad-spectrum patients with and without disease.
Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; has moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.
Poor: Has a fatal flaw, such as uses inappropriate reference standard; improperly administers screening test; biased ascertainment of reference standard; has very small sample size or very narrow selected spectrum of patients.

Source: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[48]

Appendix C. Excluded Studies

X1: Not Original Research
X2: Ineligible Population
X3: Ineligible Intervention
X4: Ineligible Comparator
X5: Ineligible Outcomes
X6: Ineligible Study Design
X7: Ineligible Language
X8: Ineligible Country
X9: Poor Quality

1. Adams S, Ehrlich R, Baatjies R, et al. Evaluating latent tuberculosis infection test performance using latent class analysis in a TB and HIV endemic setting. *Int J Environ Res Public Health*. 2019 Aug 14;16(16)doi: 10.3390/ijerph16162912. PMID: 31416206. Exclusion Code: X2.
2. Adane K, Spigt M, Dinant GJ. Tuberculosis treatment outcome and predictors in northern Ethiopian prisons: a five-year retrospective analysis. *BMC Pulm Med*. 2018 Feb 20;18(1):37. doi: 10.1186/s12890-018-0600-1. PMID: 29463234. Exclusion Code: X2.
3. Agarwal S, Nguyen DT, Lew JD, et al. Discordance between the QuantiFERON Gold In-Tube and QuantiFERON Gold Plus assays associated with country of birth TB incidence. *Tuberculosis (Edinb)*. 2019 May;116s:S2-s10. doi: 10.1016/j.tube.2019.04.005. PMID: 31060960. Exclusion Code: X5.
4. Agarwal S, Nguyen DT, Lew JD, et al. Differential positive TSPOT assay responses to ESAT-6 and CFP-10 in health care workers. *Tuberculosis (Edinb)*. 2016 Dec;101s:S83-s91. doi: 10.1016/j.tube.2016.09.012. PMID: 27727133. Exclusion Code: X2.
5. Ahmed A, Feng PI, Gaensbauer JT, et al. Interferon-γ release assays in children <15 years of age. *Pediatrics*. 2020 Jan;145(1)doi: 10.1542/peds.2019-1930. PMID: 31892518. Exclusion Code: X2.
6. Allahyartorkaman M, Mirsaeidi M, Hamzehloo G, et al. Low diagnostic accuracy of Xpert MTB/RIF assay for extrapulmonary tuberculosis: A multicenter surveillance. *Sci Rep*. 2019 Dec 6;9(1):18515. doi: 10.1038/s41598-019-55112-y. PMID: 31811239. Exclusion Code: X3.
7. Almarzooqi F, Alkhemeiri A, Aljaberi A, et al. Prospective cross-sectional study of tuberculosis screening in United Arab Emirates. *Int J Infect Dis*. 2018 May;70:81-5. doi: 10.1016/j.ijid.2018.03.001. PMID: 29526607. Exclusion Code: X2.
8. Almufty HB, Abdulrahman IS, Merza MA. Latent tuberculosis infection among healthcare workers in Duhok Province: from screening to prophylactic treatment. *Trop Med Infect Dis*. 2019 May 23;4(2)doi: 10.3390/tropicalmed4020085. PMID: 31126022. Exclusion Code: X6.
9. Altawallbeh G, Gabrielson D, Peters JM, et al. Performance of an Advanced Interferon-Gamma Release Assay for Mycobacterium tuberculosis Detection. *J Appl Lab Med*. 2021 Sep 1;6(5):1287-92. doi: 10.1093/jalm/jfab012. PMID: 33829248. Exclusion Code: X5.
10. Altet N, Dominguez J, Souza-Galvão ML, et al. Predicting the development of tuberculosis with the tuberculin skin test and QuantiFERON testing. *Ann Am Thorac Soc*. 2015 May;12(5):680-8. doi: 10.1513/AnnalsATS.201408-394OC. PMID: 25699406. Exclusion Code: X2.
11. Alvarez GG, Van Dyk D, Mallick R, et al. The implementation of rifapentine and isoniazid (3HP) in two remote Arctic communities with a predominantly Inuit population, the Taima TB 3HP study. *Int J Circumpolar Health*. 2020 Dec;79(1):1758501. doi: 10.1080/22423982.2020.1758501. PMID: 32379538. Exclusion Code: X2.
12. Alyaquobi F, AlMaqbali AA, Al-Jardani A, et al. Screening migrants from tuberculosis high-endemic countries for latent tuberculosis in Oman: A cross sectional cohort analysis. *Travel Med Infect Dis*. 2020 Sep-Oct;37:101734. doi: 10.1016/j.tmaid.2020.101734. PMID: 32437967. Exclusion Code: X4.
13. Amorim RF, Viegas ERC, Carneiro AJV, et al. Superiority of interferon gamma assay

over tuberculin skin test for latent tuberculosis in inflammatory bowel disease patients in Brazil. *Dig Dis Sci*. 2019 Jul;64(7):1916-22. doi: 10.1007/s10620-019-5475-3. PMID: 30673986. Exclusion Code: X2.

14. Ananthakrishnan R, Richardson MD, van den Hof S, et al. Successfully engaging private providers to improve diagnosis, notification, and treatment of TB and drug-resistant TB: The EQUIP Public-Private Model in Chennai, India. *Glob Health Sci Pract*. 2019 Mar 22;7(1):41-53. doi: 10.9745/ghsp-d-18-00318. PMID: 30926737. Exclusion Code: X3.
15. Arellano AL, Barriocanal AB, Valderrama A, et al. Preliminary safety results of a double-blind, randomized, placebo-controlled, clinical trial with the probiotic nyaditum resae in adults with or without latent tuberculosis infection. *Basic Clin Pharmacol Toxicol*. 2014;115:25. doi: 10.1111/bcpt.12301. PMID: CN-01091868. Exclusion Code: X3.
16. Arguello Perez E, Seo SK, Schneider WJ, et al. Management of latent tuberculosis infection among healthcare workers: 10-year experience at a single center. *Clin Infect Dis*. 2017 Nov 29;65(12):2105-11. doi: 10.1093/cid/cix725. PMID: 29020308. Exclusion Code: X2.
17. Arias-Guillén M, Sánchez Menéndez MM, Alperi M, et al. High rates of tuberculin skin test positivity due to methotrexate therapy: False positive results? *Semin Arthritis Rheum*. 2018 Dec;48(3):538-46. doi: 10.1016/j.semarthrit.2018.03.018. PMID: 29735171. Exclusion Code: X2.
18. Armenta RF, Collins KM, Strathdee SA, et al. Mycobacterium tuberculosis infection among persons who inject drugs in San Diego, California. *Int J Tuberc Lung Dis*. 2017 Apr 1;21(4):425-31. doi: 10.5588/ijtld.16.0434. PMID: 28284258. Exclusion Code: X5.
19. Arya S, Kumar SK, Nath A, et al. Synergy between tuberculin skin test and proliferative T cell responses to PPD or cell-membrane antigens of Mycobacterium tuberculosis for detection of latent TB infection in a high disease-burden setting. *PLoS One*. 2018;13(9):e0204429. doi: 10.1371/journal.pone.0204429. PMID: 30248144. Exclusion Code: X2.
20. Asadi L, Heffernan C, Menzies D, et al. Effectiveness of Canada's tuberculosis surveillance strategy in identifying immigrants at risk of developing and transmitting tuberculosis: a population-based retrospective cohort study. *Lancet Public Health*. 2017 Oct;2(10):e450-e7. doi: 10.1016/s2468-2667(17)30161-5. PMID: 29253429. Exclusion Code: X2.
21. Auguste P, Tsertsvadze A, Pink J, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. *BMC Infect Dis*. 2017 Mar 9;17(1):200. doi: 10.1186/s12879-017-2301-4. PMID: 28274215. Exclusion Code: X2.
22. Ayubi E, Doosti-Irani A, Sanjari Moghaddam A, et al. Comparison of QuantiFERON-TB Gold In-Tube (QFT-GIT) and tuberculin skin test (TST) for diagnosis of latent tuberculosis in haemodialysis (HD) patients: a meta-analysis of κ estimates - Erratum. *Epidemiol Infect*. 2018 Apr;146(5):663. doi: 10.1017/s0950268817001261. PMID: 28675138. Exclusion Code: X1.
23. Babu K, Bhat SS, Philips M, et al. Review of results of QuantiFERON TB Gold test in presumed ocular tuberculosis in a South Indian patient population. *Ocul Immunol Inflamm*. 2016 Oct;24(5):498-502. doi: 10.3109/09273948.2015.1010094. PMID: 26173028. Exclusion Code: X2.
24. Bae JH, Park SH, Ye BD, et al. Development and validation of a novel prediction model for differential diagnosis between Crohn's disease and intestinal tuberculosis. *Inflamm Bowel Dis*. 2017 Sep;23(9):1614-23. doi: 10.1097/mib.0000000000001162. PMID: 28682807. Exclusion Code: X2.
25. Baek SD, Jeung S, Kang JY. Nutritional adequacy and latent tuberculosis infection in end-stage renal disease patients. *Nutrients*. 2019 Sep 26;11(10)doi: 10.3390/nu11102299. PMID: 31561559. Exclusion Code: X5.
26. Bailey WC, Weill H, DeRouen TA, et al. The effect of isoniazid on transaminase levels. *Ann Intern Med*. 1974 Aug;81(2):200-2. PMID: 4843577. Exclusion Code: X3.
27. Bajrami R, Mulliqi G, Kurti A, et al. Comparison of GeneXpert MTB/RIF and conventional methods for the diagnosis of tuberculosis in Kosovo. *J Infect Dev Ctries*. 2016 Apr 28;10(4):418-22. doi:

10.3855/jidc.7569. PMID: 27131007. Exclusion Code: X3.
28. Balcells ME, Ruiz-Tagle C, Tiznado C, et al. Diagnostic performance of GM-CSF and IL-2 in response to long-term specific-antigen cell stimulation in patients with active and latent tuberculosis infection. *Tuberculosis (Edinb)*. 2018 Sep;112:110-9. doi: 10.1016/j.tube.2018.08.006. PMID: 30205963. Exclusion Code: X9.
29. Bao L, Li T, Diao N, et al. Fluctuating behavior and influential factors in the performance of the QuantiFERON-TB Gold In-Tube Assay in the diagnosis of tuberculosis. *PLoS One*. 2015;10(8):e0103763. doi: 10.1371/journal.pone.0103763. PMID: 26287382. Exclusion Code: X6.
30. Bapat PR, Husain AA, Daginawala HF, et al. The assessment of cytokines in Quantiferon supernatants for the diagnosis of latent TB infection in a tribal population of Melghat, India. *J Infect Public Health*. 2015 Jul-Aug;8(4):329-40. doi: 10.1016/j.jiph.2015.02.003. PMID: 25824629. Exclusion Code: X2.
31. Barcellini L, Borroni E, Brown J, et al. First evaluation of QuantiFERON-TB Gold Plus performance in contact screening. *Eur Respir J*. 2016 Nov;48(5):1411-9. doi: 10.1183/13993003.00510-2016. PMID: 27390280. Exclusion Code: X2.
32. Bastos ML, Campbell JR, Oxlade O, et al. Health system costs of treating latent tuberculosis infection with four months of rifampin versus nine months of isoniazid in different settings. *Ann Intern Med*. 2020 Aug 4;173(3):169-78. doi: 10.7326/m19-3741. PMID: 32539440. Exclusion Code: X5.
33. Bastos ML, Menzies D, Belo MT, et al. Changes in QuantiFERON®-TB Gold In-Tube results during treatment for tuberculous infection. *Int J Tuberc Lung Dis*. 2013;17(7):909-16. doi: 10.5588/ijtld.12.0927. PMID: CN-01123101. Exclusion Code: X2.
34. Batt J, Khan K. Responsible use of rifampin for the treatment of latent tuberculosis infection. *CMAJ*. 2019 Jun 24;191(25):E678-e9. doi: 10.1503/cmaj.190081. PMID: 31235488. Exclusion Code: X1.
35. Bekele A, Ashenafi S, Aderay G, et al. Latent tuberculosis among adult Ethiopian patients at chest clinic, Tikuranbessa Specialized Hospital, Addis Ababa, Ethiopia. *Ethiop Med J*. 2016 Oct;54(4):181-8. PMID: 29115115. Exclusion Code: X5.
36. Belay M, Legesse M, Mihret A, et al. IFN-γ and IgA against non-methylated heparin-binding hemagglutinin as markers of protective immunity and latent tuberculosis: Results of a longitudinal study from an endemic setting. *J Infect*. 2016 Feb;72(2):189-200. doi: 10.1016/j.jinf.2015.09.040. PMID: 26518056. Exclusion Code: X4.
37. Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2017 Nov 21;167(10):689-97. doi: 10.7326/m17-1150. PMID: 29114781. Exclusion Code: X4.
38. Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection. *Ann Intern Med*. 2017;167(10):689-97. doi: 10.7326/M17-1150. PMID: CN-01431831. Exclusion Code: X3.
39. Belo C, Naidoo S. Prevalence and risk factors for latent tuberculosis infection among healthcare workers in Nampula Central Hospital, Mozambique. *BMC Infect Dis*. 2017 Jun 8;17(1):408. doi: 10.1186/s12879-017-2516-4. PMID: 28595594. Exclusion Code: X2.
40. Biraro IA, Egesa M, Kimuda S, et al. Effect of isoniazid preventive therapy on immune responses to mycobacterium tuberculosis: an open label randomised, controlled, exploratory study. *BMC Infect Dis*. 2015 Oct 22;15:438. doi: 10.1186/s12879-015-1201-8. PMID: 26493989. Exclusion Code: X8.
41. Bisognin F, Lombardi G, Re MC, et al. QuantiFERON-TB Gold Plus with chemiluminescence immunoassay: do we need a higher cutoff? *J Clin Microbiol*. 2020 Sep 22;58(10)doi: 10.1128/jcm.00780-20. PMID: 32759352. Exclusion Code: X2.
42. Bongomin F, Ssekamatte P, Nattabi G, et al. Latent Tuberculosis Infection Status of Pregnant Women in Uganda Determined Using QuantiFERON TB Gold-Plus. *Open Forum Infect Dis*. 2021 Jun;8(6):ofab241. doi: 10.1093/ofid/ofab241. PMID: 34113689. Exclusion Code: X2.
43. Bonini S, Riccelli MG, Goldoni M, et al. Risk factors for latent tuberculosis infection

(LTBI) in health profession's students of the University of Parma. *Acta Biomed*. 2017 Mar 14;88(1s):54-60. PMID: 28327495. Exclusion Code: X4.

44. Boortalary T, Misra K, McNish S, et al. Prevalence of positive QuantiFERON gold in-tube testing in hidradenitis suppurativa. *J Dermatolog Treat*. 2018 Sep;29(6):637-40. doi: 10.1080/09546634.2018.1425360. PMID: 29325465. Exclusion Code: X2.
45. Bosco MJ, Hou H, Mao L, et al. The performance of the TBAg/PHA ratio in the diagnosis of active TB disease in immunocompromised patients. *Int J Infect Dis*. 2017 Jun;59:55-60. doi: 10.1016/j.ijid.2017.03.025. PMID: 28392318. Exclusion Code: X4.
46. Boyd R, Johnston V, Farmer B, et al. Treatment of latent tuberculosis infections in the Darwin region. *Med J Aust*. 2017 Apr 17;206(7):306-207. doi: 10.5694/mja16.01209. PMID: 28403762. Exclusion Code: X4.
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Appendix D Table 1. Studies of Sensitivity of TST for TB (KQ 2)

First Author, Year	Country (TB Burden*)	% 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
Aggerbeck, 2019[80]	South Africa (H)	64	36 (NR)	0	62	Testing occured no later than 2 weeks of starting treatment; demographic data for full study population, including those with HIV+ and those who got C-TB.	-	-	0.83 (0.75 to 0.89) (118)	Fair
Ak, 2009[76]	Turkey (I)	47.7†	34.4† (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
Altet, 2017[79]	Spain (L)	75.5	NR	6	73.1	Population characteristics extracted are for 175 active pulmonary TB patients and 41 individuals from contact tracing studies who are considered secondary TB cases. Testing likely occurred prior to treatment, because the study mentions that active pulmonary TB patients were “scheduled for anti-TB initiation” and patients were excluded if they had a previous anti-TB therapy prescription.	0.91 (NR) (216)	-	-	Fair
Berkel, 2005[62]	Netherlands (L)	NR	NR	0	39.0†	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[67]	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

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First Author, Year	Country (TB Burden*)	% 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
Choi, 2015[81]	United States (L)	65	48.1 (20.4)	6	NR	Population characteristics extracted are for all patients with active TB. Of the 300 patients, 209 have only pulmonary TB, 52 have only extrapulmonary TB, and 39 have both pulmonary and extrapulmonary TB. This is a retrospective analysis study, so patients were included if they had been diagnosed with TB "between January 2005 and March 2012 with both TST and QFT results between 60 days before and 14 days after starting treatment for TB." The QFT test used included both QFT-2G and QFT-GIT, and results were not stratified by test generation, so the outcomes are not eligible because 2G is not an eligible test.	0.86 (0.81 to 0.90) (204)	0.83 (0.77 to 0.88) (204)	-	Fair
Dilektasli, 2010[75]	Turkey (I)	NR†	36.7† (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[64]	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
Hoff, 2016[78]	South Africa (H)	65.4	Median 32 (NR)	0	12.4	Reported characteristics for HIV-negative population; only results for HIV-negative population were abstracted. Testing conducted either prior to but no later than 14 days after starting treatment.	-	0.95 (0.89 to 0.98) (146)	0.91 (0.85.3 to 0.95) (146)	Fair
Kang, 2005[58]	South Korea (I)	59.0	Median 43 Range 17 to 84	0	56.0	Study subjects had pathological or culture confirmation. Demographic data excluded 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

Appendix D Table 1. Studies of Sensitivity of TST for TB (KQ 2)

First Author, Year	Country (TB Burden*)	% 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
Mazurek, 2007[56]	United States (L)	56.8†	46.6† Median 46.4 Range 16 to 87.1	0	33.8†	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[54]	Vietnam (H)	68.9†	37.3† Range 15 to 65 or older	0.1†	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[72]	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
Park, 2017[84]	South Korea (I)	57.6	46.1 (15)	NR	58.6	Patients had either not received anti-TB treatment or had started anti-TB treatment within 1 week of the tests.	-	0.68 (NR) (33)	-	Fair
Peña, 2015[85]	Argentina (I)	85.7	34.5 (SEM)	0	100	Patients were excluded if they tested positive for HIV or other viral/bacterial infections, had multidrug-resistant TB, or had more than 7 consecutive days of anti-TB treatment.	-	0.98 (NR) (56)	-	Fair
Seibert, 1991[70]	United States (L)	67.0†	47† (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[74]	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

Appendix D Table 1. Studies of Sensitivity of TST for TB (KQ 2)

First Author, Year	Country (TB Burden*)	% 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
Tsiouris, 2006[59]	South Africa (H)	62.3†	Male† 38 Female: 36.5 (NR)	0	65.7†	Study subjects had culture confirmation. Data extracted for HIV-negative subjects.	-	0.94 (0.72 to 0.99) (16)	-	Good
Wlodarczyk, 2014[77]	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
Yu, 2015[83]	China (H)	56.9	Median 37 (NR)	0	NR	Population characteristics were extracted for patients who tested negative for HIV but positive for TB. Of the 65 patients with active TB, 60 (92.3%) had pulmonary TB, 3 (4.6%) had extrapulmonary TB, and 2 (3.1%) had both pulmonary and extrapulmonary TB. Patients were excluded if they had undergone anti-TB treatment for more than 30 days. Age IQR is 25–54.	0.81 (NR) (32)	-	-	Good
Zhu, 2019[82]	China (H)	NR	NR	NR	NR	The study did not report any general characteristics. Timing of testing with respect to treatment NR	0.66 (NR) (68)	-	-	Fair

* 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.
† Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.
Abbreviations: AFB=acid fast bacilli; BCG=bacillus Calmette-Guerin; CI=confidence interval; C-TB=RD-1-specific skin test Statens Serum Institut, Copenhagen, Denmark; HIV=human immunodeficiency virus; IQR=interquartile range; KQ-key question; NR=not reported; QFT-2G=QuantiFERON-TB Gold® test (2nd generation test); QFT-GIT=QuantiFERON-TB Gold-In-Tube® test (3rd-generation test); SD=standard deviation; SEM=standard error of the mean; TB=tuberculosis; TST=tuberculin skin test.

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Shangguan, 2020[117]	China (H)	68.9	Median 53 (NR) IQR: 37–66	4.3	NR	Population characteristics extracted (except for HIV %) are for all patients with confirmed TB, including pulmonary and extrapulmonary TB.	0.81 (NR) (833)	-	-	Fair
Lee, 2021[125]	South Korea (I)	76.2	58.3 (13.4)	NR	57.1	Patients with a history of anti-TB treatment were excluded.	-	0.78 (NR) (63)	0.83 (NR) (63)	Fair
Fukushima, 2021[116]	Japan (I)	57.7	Median 84 (NR) IQR: 76–89	0	NR	Patients were excluded if they received anti-TB drugs for more than 14 days or if their HRCT images did not indicate the presence of pulmonary TB.	0.65 (0.78 to 0.88) (142)	0.89 (0.93 to 0.99) (142)	0.93 (0.95 to 0.99) (142)	Good
Jung, 2021[126]	South Korea (I)	57.5	Median 53 (NR) IQR: 41–36	NR	NR	Included patients either had no prior anti-TB treatment or underwent treatment within the past four weeks. 33 (82.5%) of patients had active pulmonary disease with or without extrapulmonary TB, while 7 (17.5%) solely had extrapulmonary TB.	-	-	0.90 (NR) (40)	Good
Adetifa, 2007[137]	Gambia (H)	63.8	31.2 IQR 23–36	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

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Aggerbeck, 2019[80]	South Africa (H)	64	36 (NR)	0	62	Testing occured no later than 2 weeks of starting treatment; demographic data for full study population, incuding those with HIV+ and those who got C-TB.	-	0.70 (NR) (454)	-	Fair
Akashi, 2020[120]	Japan (I)	38.1	Median 43 (NR)	NR	NR	Timing of testing with respect to treatment was NR.	-	0.95 (NR) (21)	0.95 (NR) (21)	Fair
Altet, 2017[79]	Spain (L)	75.5	NR	6	73.1	Data extracted for 175 active pulmonary TB patients and 41 individuals from contact tracing studies who were considered secondary TB cases. Testing likely occurred prior to treatment, because the study mentions that active pulmonary TB patients were “scheduled for anti-TB initiation” and patients were excluded if they had a previous anti-TB therapy prescription.	0.85 (NR) (216)	0.73 (NR) (216)	-	Fair
Bae, 2016[103]	South Korea (I)	51	Age bands: ≤29 (15.6%), 30–49 (27.1%), 50–69 (35.9%), ≥70 (21.4%) (NR)	2.1	NR	The QFT-GIT population also include pulmonary (39.6%) and extra pulmonary (42.7%) or both (17.7%). All testing was performed prior to treatment. The demographics for the N=21 who had T-SPOT.*TB* were similar except a higher proportion had pulmonary TB.	0.94 (NR) (170)	0.83 (NR) (131)	-	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Bocchino, 2010[67]	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[92]	United Kingdom (L)	57.0†	NR	7.0†	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[90]	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[91]	South Korea (I)	41.1†	48.3† (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
Di, 2018[102]	China (H)	56.1	Age bands: <30 (21%), 30–60 (49%), ≥60 (29%) (NR)	NR	NR	Timing of testing with respect to treatment NR; about one third had pulmonary TB, and the rest had extrapulmonary TB. Data for results were extracted only for the n=29 who had pulmonary TB.	0.89 (NR) (29)	-	-	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Dilektasli, 2010[75]	Turkey (I)	36.7†	13.4† (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
Du, 2018[101]	China (H)	68.1	45 (NR)	NR	68.6	Only patients who had not received any antitubercular treatment were enrolled.	0.89 (0.83 to 0.93) (185)	0.88 (0.83 to 0.92) (185)	-	Fair
Erdem, 2014[139]	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[128]	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[88]	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)	-	-	Fair
Harada, 2008[135]	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.	-	0.87 (0.79 to 0.92) (100)	-	Good
Higuchi, 2009[97]	Japan (I)	78.7	52.7 Range 17–91	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)	-	-	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Hoff, 2016[78]	South Africa (H)	65.4	Median 32 (NR)	0	12.4	Reported characteristics for HIV-negative population; only results for HIV-negative population were abstracted. Testing conducted either prior to but no later than 14 days after starting treatment.	-	0.77 (0.69 to 0.83) (146)	-	Fair
Hoffmann, 2016[119]	Germany (L)	NR	NR	NR	NR	No population characteristics were given in the study; no information about timing of testing with respect to treatment.	-	0.96 (NR) (24)	0.96 (NR) (24)	Fair
Horne, 2018[118]	United States (L) and Japan (I)	61	71 (NR)	2	NR	Untreated or had received less than 14 days of antituberculosis treatment; 88% were pulmonary, 11% were extrapulmonary, and 1% were both.	-	0.92 (0.86 to 0.95) (164)	0.89 (0.83 to 0.93) (164)	Fair
Huang, 2019[149]	Taiwan (I)	61.4	56 (17.9)	NR	0	Patients were excluded if they had “loss to followup before completion of at least 6-month anti-TB therapy” (n=24) or had multidrug-resistant TB (n=15) or had BCG vaccine (n=1). The time between diagnosis and therapy was mean 1.3 days, but timing of testing with respect to treatment was NR.	-	0.66 (NR) (466)	-	Fair
Janssens, 2007[89]	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

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First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Jeon, 2013[130]	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 because of medications or advanced cancer. Subjects taking TB medication prior to exam were excluded.	-	0.65 (0.57 to 0.72) (168)	-	Fair
Jeon, 2017[144]	South Korea (I)	59.1	52 (19)	0	NR	Patients with HIV and systemic autoimmune disease, as well as those taking systemic steroids and undergoing anti-TB treatment, were excluded.	-	0.91 (NR) (159)	-	Fair
Kang, 2018[100]	China (H)	70.7	45.4 (NR)	0	58.2	Only data for sputum culture positive (N=905) were abstracted. Timing of testing with respect to treatment NR.	0.93 (0.92 to 0.95) (905)	-	-	Fair
Kiazyk, 2016[145]	Canada (L)	56.4	Median 40 (NR)	0	NR	Patients were tested within 5 days of starting anti-TB treatment. IQR for age was 31–51 years. Patients with HIV were excluded. Age was median.	-	0.78 (NR) (55)	-	Fair
Kim, 2011[61]	South Korea (I)	54.4	Median 49 Range 16–94	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)

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Kim, 2013[132]	South Korea (I)	56.5	Median 48 Range 28−86	NR	67.4	Data extracted for subjects with positive sputum culture or molecular confirmation, although 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[140]	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
Kim, 2018[113]	South Korea (I)	52.8	52.2 (16.2)	3	NR	Although the population characteristics were extracted for 36 patients with active TB, the denominator for patients with HIV infection was 32 (1 patient had an HIV infection out of 32 patients). Included both pulmonary (n=17) and extrapulmonary (n=19) sites; timing of testing with respect to treatment NR.	0.94 (0.80 to 0.99) (36)	-	-	Good
Kobashi, 2008[98]	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)	-	-	Good

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First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Kobashi, 2012[99]	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)	0.86 (0.67 to 0.95) (22)	-	Fair
Kwon, 2015[147]	South Korea (I)	56.8	Median 53 (NR)	0	NR	Patients who started medication prior to testing and had confirmed HIV antibodies were excluded. IQR for age was 35–69 years. Age was median.	-	0.86 (NR) (1,264)	-	Fair
Lai, 2011[86]	Taiwan (I)	71.0†	57.5† (18.5)	8.0†	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[93]	Taiwan (I)	51.1†	55.2† (16.4)	6.7†	NR	Data extracted for subjects with *M. tuberculosis* culture confirmation. No information available on timing of testing with respect to treatment.	0.88 (0.80 to 0.93) (98)	-	-	Fair
Lee, 2012[133]	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

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Lee, 2019[121]	Taiwan (I)	59.8	55.5 (16.1)	0	NR	None of the patients had undergone anti-TB treatment prior to the study. All of the patients had active pulmonary TB, but 10 had concomitant TB pleurisy.	-	0.64 (NR) (113)	0.66 (NR) (113)	Fair
Legesse, 2010[136]	Ethiopia (H)	54.3†	34.2† (NR)	0	20.0†	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
Lian, 2017[114]	China (H)	56.6	Median 49.29 (NR)	0	NR	Study characteristics represent the full sample of active TB patients; however, only data for subjects with pulmonary TB (n=198) were extracted for outcomes. Timing of testing with respect to treatment is NR.	0.85 (0.80 to 0.90) (198)	-	-	Fair
Lombardi, 2019[143]	Italy (L)	NR	NR	NR	NR	All adults were over 16 years old. None of the other population characteristics were reported. Patients underwent QFT-GIT testing no more than 15 days before or after the start of TB treatment.	-	0.83 (0.78 to 0.87) (324)	-	Fair
Losi, 2007[87]	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

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Manngo, 2019[124]	South Africa (H)	71.4	34.8 (12.1)	20	NR	Patients who went through TB treatment or received anti-treatment 90 days prior were excluded from the study.	-	-	0.77 (NR) (35)	Fair
Min, 2013[129]	South Korea (I)	56.8†	Median† 66 Range 27−90	NR	32.4†	Data extracted for subjects with culture confirmation. Seven 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)
Niguse, 2018[142]	Ethiopia (H)	57.4	Median 30 (NR)	15.4	29.4	Recruited participants were “naïve for highly active antiretroviral therapy (HAART) and anti-TB treatment.” Population characteristics extracted were for all active TB suspects, not just those who were culture positive. Age was median.	-	0.70 (NR) (37)	-	Fair
Pai, 2007[134]	India (H)	75.0†	36.4† Range 18−76	0	41.0†	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[54]	Vietnam (H)	68.9†	37.3† Range 15−65 years or older	0.1†	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

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Pan, 2015[110]	China (H)	64.9	Median 48.5 (NR)	0	NR	Patients with previous TB history or who had received anti-TB treatment prior to the study were excluded. Age was median. Age range was 11–91 years.	0.91 (0.89 to 0.93) (530)	-	-	Fair
Park, 2009[72]	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
Park, 2017[84]	South Korea (I)	57.6	46.1 (15)	NR	58.6	Patients had either not received anti-TB treatment or had started anti-TB treatment within 1 week of the tests.	0.94 (NR) (33)	-	-	Fair
Pathakumari, 2015[148]	India (H)	64.1	Range 19–56 (NR)	0	NR	All participants tested negative for HIV and were "naïve for antituberculosis therapy at the time of recruitment." Age range was 19–56 years.	-	0.97 (NR) (39)	-	Fair
Qian, 2013[127]	China (H)	66.2†	45.8 (17.3)†	0	84.7†	Data extracted for subjects with positive AFB smear. No subjects were receiving treatment.	-	0.82 (0.75 to 0.87) (157)	-	Fair
Qiu, 2015[112]	China (H)	64.8	46.7 (17.8)	0	NR	Study characteristics were for full group of persons with suspected TB, not just those with bacteriologic confirmation; timing of testing with respect to treatment NR.	0.90 (NR) (224)	-	-	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Ruhwald, 2011[94]	Italy (L), Denmark (L), Sweden (L), Spain (L), Greece (L), Finland (L)	57.0	Median 37 Range 18−90	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
Soysal, 2008[74]	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)	-	-	Fair
Sun, 2016[111]	China (H)	63.1	Median 44 Range 19–71 (NR)	3.1	64.6	Patients either started anti-TB therapy within 1 week or had not started therapy at all. Data extracted for the ATB group: 58 patients with pulmonary TB, 2 with spinal TB, 2 with lymph node TB, and 3 with TB meningitis. Additionally, 5 of the patients were negative for culture and AFB smear but were diagnosed with TB based on positive histopathological findings, clinical manifestations, and chest radiography.	0.91 (NR) (65)	-	-	Fair
Takasaki, 2018[107]	Japan (I)	65.7	Median 42 (NR)	0	NR	Age IQR was 29–55. Of the 99 patients with active TB, 97 (98.0%) had pulmonary TB and 9 (9.1%) had extrapulmonary TB. Patients who received anti-TB treatment within the last 14 days were excluded.	0.97 (NR) (99)	0.98 (NR) (99)	0.99 (NR) (99)	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Takeda, 2020[106]	Japan (I)	65.8	57.7 (20.9)	1.3	NR	3 patients (3.9%) were using immunosuppressive agents/steroids. Patients treated with anti-TB treatment within the past 14 days were excluded.	0.92 (NR) (76)	0.91 (NR) (76)	0.90 (NR) (76)	Fair
Taki-Eddin, 2012[138]	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
Takwoingi, 2019[104]	United Kingdom (L)	67.8	32 Range 16–81 years	5	74.3	Age was median. Data were for the full study population, not our subpopulation of interest. Testing conducted prior to treatment.	0.78 (0.69 to 0.85) (108)	0.69 (0.60 to 0.77) (106)	-	Good
Tan, 2010[96]	Taiwan (I)	75.0†	67† (12.9)	1.2†	NR	Data extracted for subjects with culture confirmation. All subjects had diabetes. Five subjects were reported to have received anti-TB treatment prior to testing, but timing of treatment was not described.	0.86 (0.72 to 0.93) (42)	-	-	Fair
Tsiouris, 2006[59]	South Africa (H)	62.3[b]	Male:† 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[95]	United States (L), Mexico (I)	T-SPOT.*TB*: 65.1 QFT-G: 67.5	T-SPOT.*TB*: Range 20−60 years or older QFT-G: Range 20−60 years or older	T-SPOT.*TB*: 7.0 QFT-G: 3.0	T-SPOT.*TB*: 87.5 QFT-G: 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)	-	-	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Wang, 2013[131]	China (H)	65.4	46 Range 20−75	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
Wang, 2018[109]	China (H)	60.9	45 (NR)	0.0	71.4	Only patients who received <1 week of standard anti-TB therapy were included in the study. The general characteristics were based on a mixed population: 21 patients diagnosed with active TB with “positive histopathological findings, clinical manifestations, and chest radiography.” Other 112 patients were culture positive and/or AFB smear positive.	0.90 (NR) (104)	-	-	Good
Waruk, 2015[146]	Kenya (H)	62.7	32 (NR)	0	NR	Population characteristics extracted were for patients who tested HIV negative and ATB positive. IQR for age was 24–35 years; no information about timing of testing with respect to treatment was reported.	-	0.84 (NR) (57)	-	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Whitworth, 2019[115]	United Kingdom (L)	67.8	Median 32 (NR)	5	74.3	Unclear when patients received anti-TB treatment; participants were included if they were "presenting with suspected tuberculosis," and baseline blood work was taken at enrollment, prior to any final diagnosis, suggesting treatment was in the early stages if taken at all.	0.85 (0.80 to 0.89) (218)	0.71 (0.64 to 0.76) (231)	-	Fair
Wlodarczyk, 2014[77]	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
Xuan, 2017[105]	China (H)	65.8	51.9 (19.7)	0	NR	Of the 450 patients, 132 (29.3%) had active TB, 257 (57.1%) did not have TB, and 61 (13.6%) previously had TB. Of the 132 patients with active TB, 76 (57.6%) had pulmonary, and only data for this group were extracted. Timing of testing with respect to treatment NR.	0.95 (NR) (76)	-	-	Fair
Yi, 2016[122]	Japan (I)	79.6	Median 59 (NR)	NR	NR	Patients who received more than 2 weeks of anti-TB treatment were excluded. Age IQR was 39–70 years. All had pulmonary TB; some also had extrapulmonary TB.	-	0.91 (0.89 to 0.97) (162)	0.77 (NR) (162)	Fair

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

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.TB Sensitivity (95% CI, Interval) (N)	QFT-GIT Sensitivity (95% CI, Interval) (N)	QFT-G Plus Sensitivity (95% CI, Interval) (N)	Quality Rating
Zhang, 2017[108]	China (H)	46.6	Median 39 (NR)	0	NR	All patients tested negative for HIV. Age IQR was 26–65 years. Patients were included if they started anti-TB treatment within 4 weeks. Included cases of both pulmonary and extrapulmonary TB.	0.95 (0.86 to 0.99) (58)	-	-	Good
Zhu, 2019[82]	China (H)	NR	NR	NR	NR	The study did not report any general characteristics. Timing of testing with respect to treatment NR.	0.97 (NR) (68)	-	-	Fair

* 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.
† Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.
Abbreviations: AFB=acid fast bacilli; ATB=active tuberculosis ; BCG=bacillus Calmette-Guerin; CI=confidence interval; C-TB=RD-1-specific skin test Statens Serum Institut, Copenhagen, Denmark; HIV=human immunodeficiency virus; IQR=interquartile range; KQ=key question; N=number analyzed; NR=not reported; PCR=polymerase chain reaction; QFT-G=QuantiFERON TB Gold® test (2nd generation test); QFT-GIT=QuantiFERON TB Gold-In-Tube® test (3rd-generation test); SD=standard deviation; SE=standard error; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

Appendix D Table 3. Studies of Specificity of TST for TB (KQ 2)

First Author, Year	Country (TB Burden*)	% 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[65]	United States (L)	41.1†	NR	NR	NR	Data extracted for study subjects at low risk for TB.	-	-	0.96 (0.87 to 0.99) (52)	Fair
Berkel, 2005[62]	Netherlands (L)	41.0	24.2 (6.1)	NR	0	Study included only patients under age 40 years and excluded patients with BCG vaccination. All study subjects were screened because of intended travel.	0.95 (0.94 to 0.96) (2,848)	0.97 (0.96 to 0.98) (2,848)	0.99 (0.98 to 0.99) (2,848)	Fair
Bienek, 2009[73]	United States (L)	83.5†	NR	0	3.3†	Data extracted for participants classified as “low risk” for TB.	-	1.00 (0.99 to 1.00) (296)	-	Fair
Fietta, 2003[64]	Italy (L)	57.1	27 (NR)	0	0	Study subjects were healthy, “low-risk” volunteers with no stated possible risk factors for *M. tuberculosis* exposure.	-	0.95 (0.84 to 0.99) (42)	-	Fair
Katsenos, 2010[71]	Greece (L)	100.0	24.3 (4.0)	NR	100.0	Population was 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) (1,750)	0.95 (0.93 to 0.95) (1,750)	0.97 (0.96 to 0.97) (1,750)	Good
Mancuso, 2012[55]	United States (L)	65.5†	21.8† (4.6)	NR	3.5†	Data extracted for subjects classified as “low risk” for TB based on history. Population was U.S. military recruits.	-	0.99 (0.98 to 0.99) (1,373)	0.99 (0.99 to 1.00) (1,373)	Fair
Mazurek, 2001[66]	United States (L)	50.0†	39† (NR)	0	NR	Data extracted for subjects at low risk for latent TB.	-	-	0.98 (0.93 to 0.99) (98)	Good
Mazurek, 2007[57]	United States (L)	94.3†	20† Median 20 Range 17−39	NR	2.2	Data extracted for subjects classified as “low risk” for TB. Population was 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
Taggart, 2004[63]	United States (L)	50.0†	31.5 (NR)	0	0	-	-	-	0.92 (0.83 to 0.97) (66)	Fair

Appendix D Table 3. Studies of Specificity of TST for TB (KQ 2)

First Author, Year	Country (TB Burden*)	% 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, 2006[60]	United States (L)	42.3†	37.3 Range 20−67	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 onsite employee health clinic. Participants originated from 20 countries.	-	-	0.96 (0.90 to 0.99) (81)	Fair
Villarino, 1999[69]	United States (L)	38.0	Median 26 Range 18−50	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) (1,555)	1.00 (0.99 to 1.00) (1,555)	Fair
Villarino, 2000[68]	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) (1,189)	1.00 (0.99 to 1.00) (1,189)	Fair

* 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.
† Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.
Abbreviations: BCG=bacillus Calmette-Guerin; CI=confidence interval; HIV=human immunodeficiency virus; KQ=key question; N=number analyzed; NR=not reported; PPD=purified protein derivative; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test.

Appendix D Table 4. Studies of Specificity of IGRA for TB (KQ 2)

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Other Study Population Comments	T-SPOT.*TB* Specificity (95% CI, Interval) (N)	QFT-GIT Specificity (95% CI, Interval) (N)	QFT-Plus Specificity (95% CI, Interval) (N)	Quality Rating
Bienek, 2009[73]	United States (L)	83.5†	NR	0	3.3†	Data extracted for participants classified as "low risk" for TB.	0.95 (0.91 to 0.97) (291)	-	-	Fair
Lempp, 2015[141]	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[55]	United States (L)	65.5†	21.8† (4.6)	NR	3.5†	Data extracted for subjects classified as "low risk" for TB based on history. Population was U.S. military recruits.	0.97 (0.96 to 0.98) (1,373)	0.99 (0.98 to 0.99) (1,354)	-	Fair
Siegel, 2018[123],	United States (L)	26.3	Median 34 (NR)	NR	0	-	-	0.99 (0.97 to 0.99) (211)	0.98 (0.95 to 0.99) (211)	Fair

* 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.
† Represents demographics of the overall study population; demographics for subjects eligible for inclusion in analysis were not reported.
Abbreviations: BCG=bacillus Calmette-Guerin; CI=confidence interval; HIV=human immunodeficiency virus; KQ=key question; NR=not reported; QFT-G=QuantiFERON TB Gold® test (2nd generation test); QFT-GIT=QuantiFERON TB Gold-In-Tube® test (3rd-generation test); SD=standard deviation; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

Appendix D Table 5. Studies of Reliability of Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Study Population Comments	Test (N)	Reliability Measure	Result	Quality Rating
Dorman, 2014[152]	United States (L)	25	Median 36 (IQR: 28–48)	0.4	9	U.S. HCWs at 4 U.S. healthcare 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 persons with TB, and healthy controls.	T-SPOT.*TB* N=91	Interrater reliability	Interrater reliability†=96% (k=0.92; p<0.05) Manual read versus automated ELISPOT reader=85.8% (k=0.73; p<0.05)	Fair
Franken, 2009[156]	Netherlands	NR	NR	NR	NR	Immigrants that were close contacts of smear-positive TB patients.	T-SPOT.*TB* N=313	Interrater reliability†	Kappas for agreement among 6 raters were all above 0.6.	Fair
Mancuso, 2012[55]	United States (L)	66	21.8	NR	3.5	Population is U.S. military recruits at low risk of exposure to TB.	TST N=1826	Interrater reliability†	Kappa=0.79	Fair
O'Shea, 2014[157]	Nepal (H)	166	NR Range 18–21	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 0.70)	Fair
Villarino 2000[68]	United States (L)	37–81‡	50	NR	NR	2 study populations: persons with pulmonary TB and those at low risk of exposure to TB.	TST (PPD S2) N=1,189	Interrater reliability†	Kappa=0.52 to 0.78 across all groups	Fair

Appendix D Table 5. Studies of Reliability of Screening Tests for Tuberculosis (KQ 2)

First Author, Year	Country (TB Burden*)	% Male	Mean Age in Years (SD)	% HIV	% BCG	Study Population Comments	Test (N)	Reliability Measure	Result	Quality Rating
Villarino 1999[69]	United States (L)	38	26	NR	NR	Persons at low risk for TB.	TST (PPD S1) N=127	Interrater reliability†	Kappa=0.69	Fair
Whitworth, 2012[150]	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 (3rd generation) N=91	Interlabora-tory reliability§	Across 3 labs, 7/91 (7.7%) subjects had discordant results (none had indeterminate results); kappas of pairwise lab sample comparisons were 0.87, 0.89, and 0.93.	Good
Whitworth, 2014[151]	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 (3rd generation) N=146	Interrater reliability	Two samples from each participant both processed via manual read and automated ELISA; across all 4 tests, 88.6% were concordant (16.0% 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 0.73–0.90)	Good

* 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.

† Agreement between first and second observer.

ǂ Among the population with pulmonary TB, 81 percent were male. Among the population at low risk of exposure to TB, 37 percent were male.

§ To measure interlaboratory reliability, three tubes of blood were collected from each subject so that the assay could be completed at three different labs noted to have "extensive experience and demonstrated proficiency."

Abbreviations: BCG=bacillus Calmette-Guerin; CDC=Centers for Disease Control and Prevention; CI=confidence interval; ELISA=enzyme-linked immunosorbent assay; GA=Georgia; HCW=healthcare worker; HIV=human immunodeficiency virus; IQR=interquartile range; KQ=key question; N=number analyzed; NR=not reported; PPD-S1 or S2=purified protein derivative standard 1 or standard 2; QFT-GIT=QuantiFERON TB Gold-In-Tube® test (3rd-generation test); SD=standard deviation; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test; TX=Texas; U.K.=United Kingdom; U.S.=United States; vs.=versus.

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Con-firmed?	Country; TB Burden*	TB Risk Factors N (%)	Mean (Range) Age	% F	% Non-White	% BCG	Quality
Gao, 2018[181] 3,738	3HP: INH up to 900 mg + RPT up to 900 mg weekly x 12 weeks; shortened to 8 weeks (1,284) $2H_2P_2$: INH up to 600 mg + RPT up to 600 mg twice a week x 8 weeks; shortened to 6 weeks (1,299) Untreated control (1,155)	24 months	50–69 years old living in rural China with a positive QFT result	Yes	China; high	Pulmonary fibrotic lesions: 64 (1.7) History of silicosis: 31 (2.41) 28 (2.16) 24 (2.08)	NR (50–69)	1,684 (45)	NR	NR	Fair
Menzies, 2004[177] 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 because of missed doses	≥18 years Positive TST following Canadian guidelines; clinician recommend 9 INH for LTBI <5% HIV positive	Yes (TST≥5, 10, and 15 mm based on risk status under Cana-dian guide-lines) Abnorma l CXR: 29 (50) 31 (53)	Canada; low	Contact with active TB case: 10 (17) 10 (17) COB high TB†: 45 (78) 48 (83) Randomization stratified by TB risk (high if HIV infected close contacts with active TB,‡ 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

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Con-firmed?	Country; TB Burden*	TB Risk Factors N (%)	Mean (Range) Age	% F	% Non-White	% BCG	Quality
Menzies, 2008[160] 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 docu-mented positive TST and if physician recom-mended INH for LTBI following national or international guidelines; 9 university hospitals (7 were in Canada)	Yes	Canada; low§ Saudi Arabia; inter-mediate, 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 Unknown: 33 25	Good

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Con-firmed?	Country; TB Burden*	TB Risk Factors N (%)	Mean (Range) Age	% F	% Non-White	% BCG	Quality
Menzies, 2018[161] 6,063 (6,012 in modified ITT)	INH 5 mg/kg of body weight, up to 300 mg/day x 9 months (3,016 randomized; 2,989 in modified ITT). RIF 10 mg/kg, up to 600 mg/day x 4 months (3,047 randomized; 3,023 in modified ITT)	28 months	18 years or older with docu-mented positive TST or interferon-γ–release assay, if they met the criteria for an increased risk of progression to active TB, and if provider recom-mended treatment with INH	Yes	Australia; low Benin; inter-mediate Brazil; high Canada; low Ghana; inter-mediate Guinea; high Indon-esia; high Saudi Arabia; inter-mediate South Korea; inter-mediate	HIV infection: 242 (4) Close contact with active TB case: 4,248 (70.7) Casual contact with active TB case: 746 (12.4) Immunosuppressi ve condition or therapy: 195 (3.2) Upper lobe fibronodular disease with area ≥2 cm: 8 (0.1)	Mean 38.4 (range NR) Age 18–35: 2,820 (46.9%) Age 36–50: 1,951 (32.5%) Age 51–90: 1,241 (20.6%)	59.1	NR	NR	Fair
Sterling, 2011[162e] 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‖	United States, Canada, Brazil, and Spain; low to high	Close contact within the past 2 years with patient with culture-confirmed TB	Median: 37‖	45.8‖	42.9‖	NR	Fair

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Con-firmed?	Country; TB Burden*	TB Risk Factors N (%)	Mean (Range) Age	% F	% Non-White	% BCG	Quality
Sterling, 2015[179] PREVENT TB 7,552	Once-weekly rifapentine 900 mg (graduated dosing for persons <50 kg) plus isoniazid 15–25 mg/kg (rounded up to nearest 50 mg; 900 mg max) given under DOT (3,893) INH 5–15 mg/kg (rounded up to nearest 50 mg; 300 mg maximum) (3,659)	4 months 10 months	Persons >12 years of age with latent *M. tuberculosis* infection	Yes	United States; low	Close contact within the past 2 years with patient with culture-confirmed TB	Median 37	45.8	42.9	NR	Fair
Sun, 2018[163] 283 random-ized; 263 analyzed	3HP (132) 9H (131)	All the participants were followed up until early termination, the developme nt of active TB, or 2 years after treatment completion	Age ≥12 years and close contacts of AFB-positive pulmonary TB patients and positive tuberculin skin test (TST) within 1 month after unprotected exposure	Yes	Taiwan; inter-mediate	Close contact with a person with confirmed TB disease: 100% Abnormal chest X-ray Abnormal but not TB: 19 (14.4) 17 (13) Smoking: 13 (9.8) 16 (12.2) Household contact: 66 (50) 60 (45.8)	37.1 ± 15 32 ± 16.4	51 (38.6) 60 (45.8)	NR	NR	Fair

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Con-firmed?	Country; TB Burden*	TB Risk Factors N (%)	Mean (Range) Age	% F	% Non-White	% BCG	Quality
Surey, 2021[180] HALT LTBI pilot study 52	RIF + INH (50 kg or less: 150/100 mg; above 50 kg: 300/150 mg) daily x 90 days (25) RPT (less than 50 kg: 750 mg; 50 kg or more: 900 mg) + INH 15 mg/kg up to 900 mg weekly x 12 weeks (27)	16 weeks	16–65 years old weighing at least 45 kg with LTBI diagnosis by IGRA or TST; 2 TB clinics in London United Kingdom	Yes	United Kingdom; inter-mediate	Diabetes: 1 (4) 1 (3.7) Immuno-suppressant medication: 0 (0) 1 (3.7)	32.5 (17–58) 38.2 (23–56)	12 (48) 14 (51.8)	NR	NR	Fair
Thompson, 1982[159] 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¶ with fibrotic pulmonary lesions# not previously treated with anti-TB medications	Yes (6 mm or greater Mantoux test)**	7 European countries†† low to inter-mediate	NR	Median 50 years (NR); 38% were between 55 and 65 years	47	NR	NR	Good (for KQ 3) Fair (for KQ 5)

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

Author, Year Trial Name N	Drug, Dose x Duration (N)	Followup	Population	LTBI Con-firmed?	Country; TB Burden*	TB Risk Factors N (%)	Mean (Range) Age	% F	% Non-White	% BCG	Quality
White, 2012[178] 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 because of missed doses, unless necessary to restart (RIF, restart if missed doses >2 weeks); INH restart if missed doses >1 month	Inmates ≥18 years in the San Francisco City and County Jail diagnosed with LTBI at jail entry	Yes, diag-nosis method NR	United States: 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

* 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/100,00.
† Countries classified as high TB burden according to TB incidence as suggested by the World Health Organization.
ǂ Number of subjects who had been in close contact with an individual with active tuberculosis unspecified.
§ Although TB burden in Canada is low, 54–55 percent of the Canadian participants (a total of 462 participants) were born in countries with high TB incidence.
ǀ Data extracted from supplemental data provided by personal communication source for eligible study subgroup (HIV-negative subjects with IGRA or TST confirmation).
¶ Inclusion criteria initially limited to age 20–64 years, but a few persons were included outside these limits.
# Defined as well-delineated radiographic lesions of probable TB 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).
** Median induration of participants was 15 mm (range 6–90 mm).
†† Czechoslovakia (low), Finland (low), Germany (low), Hungary (intermediate), Poland (intermediate), Romania (intermediate), Yugoslavia (low-intermediate).
Abbreviations: $2H_2P_2$=twice-weekly INH up to 600 mg and RPT up to 600 mg for 8 weeks; 3HP=3 months weekly rifapentine plus INH; 9h=9 months of daily directly observed INH alone; AFB=acid fast bacilli; BCG=bacillus Calmette-Guérin vaccine; COB=country of birth; CXR=chest X-ray; DOT=directly observed therapy ; F=female; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assays; INH=isoniazid; ITT=intention to treat; IUAT=International Union Against Tuberculosis and Lung Disease;

Appendix D Table 6. Characteristics of Included Randomized, Controlled Trials (KQs 3, 5): Main Analysis

KQ=key question; LTBI=latent tuberculosis infection; N=sample size; NR=not reported; QFT=QuantiFERON-TB; RIF=rifampin; SD=standard deviation; TB=tuberculosis; TST=tuberculin skin test; Unk=unknown.

Appendix D Table 7. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Benefits (KQ 3)

First Author, Year Trial Name N	Drug, Dose X Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden*	TB Risk Factors	Mean Age in Years (SD)	% Male	% Non-White	% BCG	Quality
Bush, 1965[165] All subjects: 2,238 ≥15 years 1,309 ≥20 years 1,140	INH 250 mg/day x 12 months (571) Placebo (569)	1 year after end of medication regimen	Subjects ≥20 years who were HH contacts of active TB cases Total HHs: 328 322 HHs ≥1 cases active TB: 220 189 Study population ≥20 years: 569 571 Study population ≥15 years: 646 663	No, but chest film and TST (5 TU PPD-S); 90% of the adults with ≥5 mm TST	Japan: low	HH contacts (all ages) who lived with an adult index case >9 months: (78.5) (78.9)	Subjects 20–49 years: 818 Subjects 50+ years: 322	Of subjects ≥20 years: 40.1 41.1	NR; approx-imate-ly 100%	NR	Fair
Falk, 1978[166, 184] 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†, ‡	NR; required to have inactive pulmonary TB	U.S.: low	NR	78% were 30–50; 16% were 51–70	98.2	23.5 22.9 21.4	NR	Fair

Appendix D Table 7. Characteristics of Randomized, Controlled Trials Used Only in Sensitivity Analyses for Benefits (KQ 3)

First Author, Year Trial Name N	Drug, Dose X Duration (N)	Followup	Population	LTBI Confirmed?	Country; TB Burden*	TB Risk Factors	Mean Age in Years (SD)	% Male	% Non-White	% BCG	Quality
Ferebee, 1963[167] 27,924 patients (566 psychiatric wards randomized); 25,210 patients included in morbidity analyses[§, ‖]	INH 4-7 mg/kg/day (average of 5mg/kg)[¶] 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.[#]: low	Residing in institutions 100% Abnormal CXR 1216 (9.5%) 1071 (8.7%) Tuberculin positive 7242 (56%) 7253 (59%)	Males: 48 Females: 54 Range: 2–80+ years	48.8 46.4	13.1 11.4	NR	Fair
Veening, 1968[168] 261	INH 600 mg (8-10 mg/kg) x 4 months, then 400 mg (5-7mg/kg) until 1 year (133)[**] 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 old at baseline	100 100	NR	NR	Poor

[*] TB burden according to World Health Organization classification. Low <10 cases/100,000; intermediate 10–99 cases/100,000; high >100 cases/100,000.
[†] Determine by NTA diagnostic standards current at that time.
[ǂ] TB had been inactive for 5 years or more in 95 percent of participants.
[§] Morbidity analyses did not include patients who moved to a new ward and crossed over; only included persons who took either INH or placebo.
[‖] All data entered for Ferebee 1963 for subsequent rows of this table are based on the N included in morbidity analyses.
[¶] Those 15 and older received 300 mg/day.
[#] Wisconsin, Georgia, Michigan, and Massachusetts.
[**] This is a higher dose than is currently recommended by CDC.

Abbreviations: ATS=American Thoracic Society; BCG=bacillus Calmette-Guérin vaccine; CXR=chest x-ray; F=female; HH=household; INH=isoniazid; kg=kilogram; LTBI=latent tuberculosis infection; mg=milligram; 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; U.S.=United States.

Appendix D Table 8. Results 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[160] 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)
Menzies, 2018[161] 6,063 (6,012 in modified ITT)	INH 5 mg/kg of body weight, up to 300 mg/day x 9 months (3,016 randomized; 2,989 in modified ITT) RIF 10 mg/kg, up to 600 mg/day x 4 months (3,047 randomized; 3,023 in modified ITT)	9 (0.30) 8 (0.26)	NR	NR	14 (0.46) 22 (0.72)	Adverse event, trial drug stopped permanently: 4 (0.1) 0 (0) Trial drug stopped permanently for grade 3–5 event: 1 (<0.1) 0 (0)
Sterling, 2011[162] 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
Sun, 2018[163] 263	3HP (132) 9H (131)	NR	NR	NR	0 (0) 0 (0)	0 (0) 0 (0)

Appendix D Table 8. Results 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 (%)
Thompson, 1982[159] 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) Percent reduction compared with placebo*, † 21 65 75 NA (reference) RR compared with 52 weeks of INH‡ 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§, ‖ 2.1 NA (reference)	NR	NR	All groups combined: 1,124 (4.0) NR by group	Due to tuberculosis: 0 (0.00) 0 (0.00) 0 (0.00) 3 (0.042)

* Percentage 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).

† When limited to "completer-compliers," the percentage reductions were 31, 69, 93, and NA (reference), respectively.

‡ 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.

§ 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.

‖ When limited to "completer-compliers," the RRs were 9.4, 4.3, 1.0 (reference), and 13.6, respectively.

Abbreviations: 3HP=rifapentine plus INH ; 9H=9 months of daily directly observed INH alone; CI=confidence interval; INH=isoniazid; ITT=intention to treat; IUAT=International Union Against Tuberculosis and Lung Disease; KQ=key question; N=sample size; NA=not applicable; NR=not reported; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis.

Appendix D Table 9. Results 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 (%)*
Gao, 2018[181] 3,738	3HP: INH up to 900 mg + RPT up to 900 mg weekly x 12 weeks; shortened to 8 weeks (1,284) $2H_2P_2$: INH up to 600 mg + RPT up to 600 mg twice a week x 8 weeks; shortened to 6 weeks (1,299) Untreated control (1,155)	77 (6.0) 82 (6.31)	13 (1.02) 15 (1.17) p=0.704	0 (0) 0 (0)	110 (8.60) 66 (5.16) p=0.006	Hypersensitivity or allergy: 43 (3.36) 65 (5.08) p=0.031 Influenza-like symptoms: 46 (3.60) 29 (2.27) p=0.046
Menzies, 2004[177] 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)†	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)‡

Appendix D Table 9. Results 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 (%)*
Menzies, 2008[160] 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§,‖,¶,#,** 7 (1.7) 17 (4.0) RD -2.3% (95% CI, -5.0 to -0.1) Subtotal for any grade 1 or 2 AE: ††, ‡‡, §§, ‖‖, ¶¶ 9 (2.1) 7 (1.6) RD 1% (95% CI, 1.0 to 3.0)	Grade 3 or 4 hepatotoxicity:§ 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 AEs):‖ 1 (0.2) 2 (0.5) Calculated RR: 0.51 (95% CI, 0.05 to 5.59)	Hematologic (grade 3 or 4 AEs):§ 2 (0.5) 1 (0.2) Calculated RR: 2.0. (95% CI, 0.19 to 22.34) Drug interaction (grade 3 or 4 AEs):** 1 (0.2) 0 (0) Calculated RR: 3.05 (95% CI, 0.13 to 74.66) Rash (grade 3 or 4 AEs)‖ 1 (0.2) 0 (0) Calculated RR: 3.05 (95% CI, 0.13 to 74.66) Rash (grade 1 or 2 AEs)‡‡ 8 (1.9) 5 (1.2) Calculated RR: 1.63 (95% CI, 0.54 to 4.93)

Appendix D Table 9. Results 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 (%)*
Menzies, 2018[161] 6,063 (6,012 in modified ITT)	INH 5 mg/kg of body weight, up to 300 mg/day x 9 months (3,016 randomized; 2,989 in modified ITT) RIF 10 mg/kg, up to 600 mg/day x 4 months (3,047 randomized; 3,023 in modified ITT)	Grade 3–5: 75 (2.3) 31 (0.9) RD: -1.4 (-2.0, -0.8) Data for Phases 2 and 3 trials combined (total n=3,416 for INH and n=3,443 for RIF)	65 (2.0) 11 (0.3) RD: -1.7 (-2.2, -1.2) Data for Phases 2 and 3 trials combined (total n=3,416 for INH and n=3,443 for RIF)	1 (0.0) 0 (0) RD: 0 (-0.1, 0.0) Data for Phases 2 and 3 trials combined (total n=3,416 for INH and n=3,443 for RIF)	1 (0) 3 (0.1) RD: 0.1 (95% CI, -0.1 to 0.2) Data for Phases 2 and 3 trials combined (total n=3,416 for INH and n=3,443 for RIF)	Hematologic 0 (0.0) 6 (0.2) RD: 0.2 (95% CI, 0.1 to 0.3) Drug interaction 0 (0) 2 (0.1) RD: 0.1 (95% CI, -0.1 to 0.2) Rash 2 (0.1) 6 (0.2) RD: 0.1 (95% CI, -0.1 to 0.3) Other AE 4 (0.1) 1 (0.0) RD: -0.1 (-0.2, 0.0) Data for Phases 2 and 3 trials combined (total n=3,416 for INH and n=3,443 for RIF)
Sterling, 2011[162, ***] 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:††† 176 (4.9) 184 (5.5) Calculated RR: 0.90 (95% CI, 0.73 to 1.10) Grade 4 toxicity:††† 34 (1.0) 35 (1.1) Calculated RR: for Grade 3 or 4 toxicity: 0.90 (95% CI, 0.75 to 1.08)	NR for hepatotoxicity specifically Grade 5 (death, from any cause): 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)

Appendix D Table 9. Results 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 (%)*
Sterling, 2015[179] PREVENT TB 7,552	Once-weekly rifapentine 900 mg (graduated dosing for persons <50 kg) plus isoniazid 15–25 mg/kg (rounded up to nearest 50 mg; 900 mg max) given under DOT (3,893) INH 5–15 mg/kg (rounded up to nearest 50 mg; 300 mg maximum) (3,659)	NR	Hepatotoxicity attributable to study drug: 17 (0.43) 97 (2.7)	NR	Among the 153 systemic drug reactions: 7 (0.17) 1 (0.03)	Any clinically significant systemic drug reaction: 138 (3.5) 15 (0.04) Among the 153 systemic drug reactions, characterization: Cutaneous: 23 9 Flu-like: 87 2 Respiratory: 5 0 Not defined: 16 3

Appendix D Table 9. Results 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 (%)*
Sun, 2018[163] 263	3HP (132) 9H (131)	12 (9.1) 7 (5.3)	AST, ALT > 2 ULN 8 (6.1) 15 (11.5) AST, ALT > 3 ULN and T-bil > 2 mg/dL 6 (4.5) 13 (9.9) AST, ALT > 5 ULN and T-bil > 3 mg/dL 2 (1.5) 4 (3.1) AST, ALT > 10 ULN and T-bil > 5 mg/dL 0 (0) 3 (2.3) "Clinically relevant hepatotoxicity" 2 (1.5) 7 (5.3)	0 (0) 0 (0)	Abdominal pain 4 (3.0) 3 (2.3) Diarrhea 2 (1.5) 3 (2.3) Nausea 12 (9.1) 9 (6.9) Vomiting 10 (7.6) 1 (0.8)	Systemic drug reaction 5 (3.8) 0 (0) Flu-like symptoms: Fatigue 23 (17.4) 14 (10.7) Dizziness 10 (7.6) 7 (5.2) Fever 17 (12.9) 1 (0.8) Chills 6 (4.5) 1 (0.8) Hot flush 8 (6.1) 1 (0.8) Headache 10 (7.6) 1 (0.8) Myalgia 3 (2.3) 0 (0) Dyspnea 2 (1.5) 2 (1.5) Cutaneous reaction 14 (10.6) 9 (6.9)

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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 (%)*
Sun, 2018[163] 263 (continued)						Hypersomnia 9 (6.8) 5 (3.8) Others 13 (9.8) 4 (3.1)
Surey, 2021[180] HALT LTBI pilot study 52	RIF + INH (50 kg or less: 150/100 mg; above 50 kg: 300/150 mg) daily x 90 days (25) RPT (less than 50 kg: 750 mg; 50 kg or more: 900 mg) + INH 15 mg/kg up to 900 mg weekly x 12 weeks (27)	Withdrawn from trial due to LFTs > 3 ULN and symptomatic: 1 (4) 0 (0)	Clinically significant raised ALT: 4 (16) 3 (11.1)	0 (0) 0 (0)	NR	NR

Appendix D Table 9. Results 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 (%)*
Thompson, 1982[159] 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)[183] Due to AEs (GI distress, liver disease, or gallbladder disease): INH (1.8) Placebo (1.2)[183] DC due to liver disease: INH (0.4) Placebo (0.1)[183]	Hepatitis: INH 99‡‡‡ (0.5) Placebo 7 (0.1) Cumulative excess hepatitis rates per 1,000 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 1,000 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)[183] 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 9. Results 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 (%)*
White, 2012[178] 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) 19 (10)	Other AEs:‡ 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‖ 13 (7) 14 (8) Calculated RR: 0.95 (95% CI, 0.46 to 1.96)

* No studies reported peripheral neuropathy or development of drug-resistant TB outcomes.
† Other adverse events were not presented by drug regimen, but for entire population.
‡ 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.
§ 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.
‖ Criteria for a grade 3 rash is a rash that affects 100 percent of body surface area or mucus membranes, conjunctivae are affected, vital signs are abnormal (fever or low blood pressure), or there is wheezing.
¶ 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.
# Protracted nausea and vomiting or severe abdominal pain that disrupts daily life (e.g., cannot sleep) and severe diarrhea (more than five bowel movements per day) met the criteria for a grade 3 gastrointestinal adverse event.
** 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.
†† 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.
‡‡ Criteria for a grade 1 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 percent of total body surface area or rash is confluent in areas.

Appendix D Table 9. Results of Included Randomized, Controlled Trials for Harms (KQ 5): Main Analysis

§§ 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 and 2.
ǁǁ Some stomach upset with nausea or loss of appetite, but no vomiting and no change in bowel habits met criteria for a grade 1 gastrointestinal adverse event.
¶¶ 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 occurred, and therapy did not have to be changed.
Data extracted from supplemental data provided by personal communication source for eligible study subgroup (HIV-negative subjects with IGRA or TST confirmation).
*** 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.
††† Common toxicity criteria version 2.0. Bethesda, MD: Cancer Therapy Evaluation Program, 1999 (http://www.eortc.be/services/doc/ctc/ctcv20_40–992.pdf).
ǂǂǂ The total number of hepatotoxicity cases among isoniazid patients was calculated based on the cumulative excess hepatitis rates per 1,000 cases for INH presented in the paper.
Abbreviations: $2H_2P_2$=twice-weekly INH up to 600 mg and RPT up to 600 mg for 8 weeks; 3HP=rifapentine plus INH; 9H=9 months of daily directly observed INH alone; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; DC=discontinuation; DOT=directly observed therapy; GI=gastrointestinal; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; INH=isoniazid; ITT=intention to treat; IUAT=International Union Against Tuberculosis and Lung Disease ; KQ=key question; LFT=liver function test; LTBI=latent tuberculosis infection; MD=Maryland; N=sample size; NR=not reported; RD=risk difference; RIF=rifampin; RPT=rifapentine; RR=relative risk; TB=tuberculosis; T-bil=total bilirubin; TST=tuberculin skin test; ULN=upper limit of normal.

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

First Author, Year	Were selection criteria (for patients) clearly described?	Was the spectrum of patients included in the study representative of the patients who will receive the test in primary care?	Were withdrawals and missing data from the study adequately explained or not present?	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 (i.e., each test interpreted blinded to the result of the other)?	Were methods for calculating accuracy (e.g. sensitivity/ specificity) clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how indeterminate results were handled?	Quality Rating
Adetifa, 2007[137]	Partially	NA	Partially	Partially	Yes	NR	NA	Yes	Fair
Aggerbeck, 2019[80]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Fair
Ak, 2009[76]	Yes	NA	NA	Yes	Yes	NR	Yes	Yes	Good
Akashi, 2020[120]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes (in the discussion)	Fair
Altet, 2017[79]	Yes	NA	NR	Yes	Yes	NR	Yes	Yes	Fair
Bae, 2016[103]	Yes	NA	NR	Yes	Yes	NR	Yes	Yes	Fair
Balcells, 2018[217]	Yes	NA	No; high missing data for the portion relevant for this review and is not explained (38/72 missing)	Yes	Yes	NR	No (unclear why many active TB cases were not in the calculations for positive cases)	No	Poor
Bellete, 2002[65]	Partially	Yes	Yes	Yes	NA	NA	NA	NA	Fair
Berkel, 2005[62]	Yes	No	NA	No	No	NR	Partially	NA	Fair
Bienek, 2009[73]	Yes	Partially	Yes	Yes	NA	NR	Partially	Yes	Fair
Bocchino, 2010[67]	Partially	NA	NA	No	Yes	NR	NA	Yes	Fair
Boyd, 2011[92]	Yes	NA	NA	Yes	Yes	Yes	Yes	Yes	Good
Bua, 2007[218]	No	NR	NA	Partially	NA	NR	NA	Yes	Fair
Chedid, 2020[219]	Partially	NA	No	Yes	Yes	NR	NA	No	Poor
Chee, 2008[90]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Good

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Chen, 2016[220]	No (retrospective, and all it provides is "consecutive pregnant women with suspected TB")	NA	No	No (no description of how testing was done)	NR	NR	NA	No	Poor
Cho, 2011[91]	Yes	NA	NA	Partially	Yes	Yes	Yes	Yes	Good
Choi, 2015[81]	Yes	NA	NR	Yes (but QFT-G is not eligible)	NR	NR (but unlikely in retrospective study)	NA (raw data given)	Yes (13 persons excluded for indeterminate results)	Fair
Cummings, 2009[158]	No	Partially	No	Yes	NA	NR	No	Yes	Poor
Dewan, 2007[221]	Yes	NA	Partially	Yes	Yes	NR	Yes	Yes	Fair
Di, 2018[102]	Yes	NA	Yes	Yes	Yes	NR	NA (raw data given)	No	Fair
Dilektasli, 2010[75]	Yes	Partially	Yes	Partially	Yes	Partially	NA	Yes	Fair
Dorman, 2014[152]	Yes	No	Yes	Yes	NA	NR	Yes	Yes	Good
Du, 2018[101]	Yes	NA	Yes	Yes	Yes	NR	NA (raw data given)	Yes (indeterminate number reported)	Fair
Erdem, 2014[139]	No	NA	NA	Yes	No	NR	No	NR	Fair
Eum, 2008[222]	Partially	NA	No	Yes	Yes	NR	Partially	No	Poor
Feng, 2013[128]	Partially	NA	Yes	Yes	Partially	NR	NA	Yes	Fair
Fietta, 2003[64]	Yes	Yes	NA	Yes	NR	NR	NA	NA	Fair
Franken, 2007[223]	No	No	No	Partially	NA	NR	Partially	No	Poor

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Franken, 2009[156]	Yes	Partially	NA	Yes	NA	NR	NA	Yes	Fair
Fukushima, 2021[126]	Yes	NA, NR	Yes	Yes	Yes	NR	NA	Yes	Good
Goletti, 2006[88]	Yes	NA	NR	Partially	Yes	Yes	Yes	Partially	Fair
Han, 2016[224]	No	NA	No	No (not adequately described)	NR	NR	NA (raw data reported)	No	Poor
Harada, 2008[135]	Yes	NA	NA	Yes	Yes	NR	NA	Yes	Good
He, 2015[225]	Yes	NA	Yes	Yes	Yes	NR	Partially	No	Fair
Higuchi, 2009[97]	Partially	NA	Yes	Yes	Yes	NR	NA	Yes	Fair
Hoff, 2016[78]	Yes	NA	Yes	Yes	Yes	NR (double-blind between TST and another skin test that was not eligible, but NR for our comparisons of interest)	NA (raw data reported)	Yes	Fair
Hoffmann, 2016[119]	Yes	NA	Yes	Yes	NR	NR	NA (raw data reported)	Yes (they call them invalid)	Fair
Horne, 2018[118]	Yes	NA	NR	Yes	Yes	NR	NA (raw data reported)	Yes	Fair
Huang, 2019[149]	Partially, unclear timing of testing with respect to treatment	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR
Janssens, 2007[89]	Yes	NA	NA	Yes	Yes	NR	Yes	No	Fair

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Jeon, 2013[130]	Yes	NA	NA	Yes	Yes	NR	NA	No	Fair
Jeon, 2017[144]	Partially, unclear timing of testing with respect to treatment	NA	Unclear, retrospective analysis based on available data	Yes	Yes	NR	NA	Yes	Fair; blinding NR, unclear missing data
Jung, 2021[126]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Good
Kalantri, 2009[226]	No	NA	NA	Yes	Yes	NR	NA	No	Poor
Kamiya, 2013[227]	No	NA	Partially	Yes	Partially	NR	Yes	NA	Poor
Kang, 2005[58]	Partially	NA	NR	Yes	Partially	No	Partially	Yes	Fair
Kang, 2007[228]	Partially	NA	NA	Partially	Partially	NR	No	No	Poor
Kang, 2018[100]	Yes	NA	Yes; not present	Yes	Yes	NR	NA, raw data provided	NR	Fair
Katsenos, 2010[71]	Yes	Partially	NA	Yes	NA	Yes	Yes	Yes	Good
Kiazyk, 2016[145]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR
Kim, 2011[61]	Yes	NA	NA	Yes	Yes	NR	NA	Partially	Good (QFT-GIT) Poor (TST)
Kim, 2013[132]	Partially	Yes	NA	Yes	Partially	NR	Yes	Yes	Fair
Kim, 2014[140]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Good
Kim, 2018[113]	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good
Kobashi, 2008[229]	Partially	NA	Yes	Yes	Yes	NR	NA	Yes	Fair
Kobashi, 2008[230]	Partially	NA	NA	Yes	Yes	NR	NA	Yes	Fair
Kobashi, 2008[98]	Yes	NA	NA	Yes	Yes	NR	NA	Yes	Good
Kobashi, 2009[231]	No	NA	NA	Partially	Yes	NR	NA	No	Poor

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Kobashi, 2009[232]	Partially	NA	NA	Yes	Yes	NR	No	Partially	Fair
Kobashi, 2012[99]	Yes	NA	Yes	Partially	Yes	NR	Yes	Yes	Fair
Kwon, 2015[147]	Yes	NA	Unclear; retrospective analysis with QFT testing up to individual clinician	Yes	Yes	NR	NA	Yes	Fair; blinding NR, unclear missing data
La Distia Nora, 2018[233]	Yes	NA	No (data missing for 21% of TST)	Yes	No (micro exams only done in selected cases)	NR	NA	NA	Poor; missing data; lack of blinding, not all persons got same reference standard
Lai, 2011[86]	Partially	NA	NA	Partially	Yes	NR	NA	Yes	Fair
Lai, 2011[93]	Partially	No	NA	Yes	Yes	NR	Yes	Yes	Fair
Lee, 2011[234]	Partially	No	NA	Partially	Yes	NR	NA	NR	Fair
Lee, 2012[133]	Partially	NA	NA	Yes	Yes	Yes	Yes	Yes	Good
Lee, 2019[121]	Yes	NA	Yes; not present	Yes	Yes	NR	NA, raw data provided	Yes, raw data and enough information on handling	Fair
Lee, 2021[125]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Fair
Legesse, 2010[136]	Yes	No	NA	Yes	Yes	NR	Yes	Yes	Fair
Lempp, 2015[141]	No	NA	NA	Yes	No	NR	No	NR	Fair
Li, 2012[235]	Partially	NA	NA	Partially	No	Partially	Yes	Yes	Poor

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Li, 2019[236]	Partially; timing of testing with respect to treatment was NR	NA	No (retrospective analysis and 23% of subjects were missing T-SPOT.*TB* tests)	Yes	Yes	NR	NA	Yes	Poor; missing data, blinding NR
Lian, 2017[114]	Partially; unclear timing of testing with respect to treatment	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR
Liu, 2020[237]	Yes	NA	Partially	Yes	Unclear	NR	No	No	Poor
Liu, 2021[238]	Yes	NA	No; high missingness	Yes	Yes; required in inclusion criteria	NR	NA	Partially	Poor
Lombardi, 2019[143]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR
Losi, 2007[87]	Partially	NA	NA	Partially	Yes	NR	Yes	Partially	Fair
Lui, 2011[239]	Yes	No	NA	Yes	Partially	Partially	Yes	Yes	Fair
Mancuso, 2012[55]	Partially	No	Yes	Yes	NA	Yes	Partially	No	Fair
Manngo, 2019[124]	Yes	NA	Yes	Yes	Yes	Unclear	NA	Yes	Fair
Mazurek, 2001[66]	Yes	Yes	NA	Yes	NA	NA	NA	NA	Good
Mazurek, 2007[56]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Good
Mazurek, 2007[57]	Yes	Yes	Yes	Yes	NA	NR	No	No	Fair
Memish, 2000[240]	No	NA	NA	No	NR	NR	NA	NA	Poor
Metcalfe, 2010[241]	Yes	NA	Yes	Yes	Partially	NR	Partially	Yes	Fair

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Min, 2013[129]	No	NR	NA	Yes	Yes	NR	Yes	Partially	Poor (Sp) Fair (Sn)
Niguse, 2018[142]	Yes	NA	No	Yes	Yes	NR	NA	Yes	Fair; 213 enrolled, but only 202 described in the analysis without any explanation; blinding NR
O'Shea, 2014[157]	Yes	No	NA	Yes	Yes	NR	Yes	Partially	Fair
Ozekinci, 2007[242]	Partially	Yes	NA	No	Yes	NR	No	Yes	Poor
Pai, 2007[134]	Yes	NA	Yes	Yes	Yes	NR	Yes	Yes	Good
Painter, 2013[54]	Yes	NA	Partially	Yes	Yes	Yes	Partially	No	Fair
Palazzo, 2008[243]	Partially	Partially	No	No	Yes	NR	Partially	No	Poor
Pan, 2015[110]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes (appears no indeterminates were observed)	Fair; blinding NR
Park, 2009[72]	Partially	Partially	Yes	Partially	Partially	NR	Partially	Yes	Fair
Park, 2017[84]	Yes	NA	Unclear, retrospective analysis so only persons with data available were included	Yes for T.SPOT.*TB*; no for TST	Yes	NR	NA	No	Fair; blinding NR; no des-cription of TST; retro-spective analysis so no data on withdrawals/ missing data

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Pasticci, 2021[244]	Yes	NA	No	Yes	Yes	NR	NA	No	Poor
Pathakumari, 2015[148]	Partially (limited information provided, specifically timing of testing vs. starting of treatment)	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR; limited information about study subjects
Peña, 2015[85]	Yes	NA	Yes	Yes	Yes	No (administered by medical staff so unlikely they would have been blinded)	NA	NA	Fair; lack of blinding
Piotrowski, 2018[245]	Partial	Partial	Yes	Yes	NA	NR	NA	No; although methods state they looked at indeterminate results, only positives and negatives were reported.	Poor; a small sample, handling of indeterminate results could have major effect on estimate
Qian, 2013[127]	Yes	NA	NA	Yes	Yes	NR	NA	No	Fair
Qiu, 2015[112]	Yes	NA	Yes	Yes	No	Yes	NA	Yes	Fair; appears less than half met bacteriologic criteria
Ra, 2011[246]	Partially	No	NA	Partially	Yes	NR	No	Yes	Fair (QFT-G) Poor (TST)
Ruhwald, 2011[94]	Yes	Partially	NA	Yes	Yes	NR	NA	Yes	Good

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Salindri, 2019[247]	Partially (retrospective analysis so no information on timing of testing with respect to treatment)	NA	No (only 68% had TST results and additional persons excluded for incomplete followup with respect to treatment outcomes)	Yes	Yes	No (retrospective study so staff administering TST unlikely to have been blinded to status)	NA	NA	Poor
Seibert, 1991[70]	Partially	NA	Partially	Yes	Yes	NR	NA	NA	Fair
Shalabi, 2009[248]	Partially	NR	NA	No	Yes	NR	NA	NA	Poor
Shangguan, 2020[117]	Yes	NA	Yes; adequately explained ~10%	Yes	Yes; required in inclusion criteria	NR	NA	Yes	Fair
Shrestha, 2011[249]	No	NA	NA	Partially	Yes	NR	NA	Yes	Poor
Siegel, 2018[123]	Yes	Yes	Yes	Yes	NA	NR	NA	Yes	Fair; blinding NR
Soysal, 2008[74]	Yes	Partially	No	Yes	Yes	NR	Partially	Partially	Fair
Sun, 2016[111]	Yes	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR
Taggart, 2004[63]	Partially	Yes	Yes	Yes	NA	NA	NR	NA	Fair
Taggart, 2006[60]	Yes	Partially	NA	Yes	NA	NR	Partially	No	Fair
Takasaki, 2018[107]	Yes	No; TB-specific hospital, mostly female, mostly young	Yes; not present	Yes	Yes	NR	NA; raw data provided	Yes; adequately explained	Fair

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

First Author, Year	Were selection criteria (for patients) clearly described?	Was the spectrum of patients included in the study representative of the patients who will receive the test in primary care?	Were withdrawals and missing data from the study adequately explained or not present?	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 (i.e., each test interpreted blinded to the result of the other)?	Were methods for calculating accuracy (e.g. sensitivity/ specificity) clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how indeterminate results were handled?	Quality Rating
Takeda, 2020[106]	Partially	NA	Yes; not present	Partially; yes for T-SPOT.*TB*, unclear for IGRAs	Yes	NR	NA; raw data provided	Yes; indeterminate results were excluded, but only 3% of total	Fair
Taki-Eddin, 2012[138]	Partially	NA	NA	Yes	Yes	NR	NA	NR	Fair
Takwoingi, 2019[104]	Yes	NA	Yes; adequately explained	Yes	Yes	Yes	NA; raw data provided	Yes; adequately explained	Good
Tan, 2010[96]	Partially	NA	NA	Yes	Yes	NR	NA	Yes	Fair
Tang, 2020[250]	Partially	NA	No; study merely states missing data were "due to the influence of objective conditions and personal will of subjects." Only 30 of 37 ATB had QFT+ results.	Yes	Yes	NR	No	No	Poor; missing data not explained; most of population was HCWs, no information on blinding of test interpreters
Telisinghe, 2017[251]	Yes	NA	Yes; not present	Yes	Yes	NR	NA; raw data provided	Yes	Fair
Tsiouris, 2006[59]	Yes	NA	NR	Yes	Yes	Yes	Yes	Yes	Good
Turtle, 2012[252]	No	NA	Partially	Partially	NR	NR	No	No	Poor
Villarino, 1999[69]	Partially	Partially	Yes	Yes	NA	Partially	NA	Partially	Fair

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

First Author, Year	Were selection criteria (for patients) clearly described?	Was the spectrum of patients included in the study representative of the patients who will receive the test in primary care?	Were withdrawals and missing data from the study adequately explained or not present?	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 (i.e., each test interpreted blinded to the result of the other)?	Were methods for calculating accuracy (e.g. sensitivity/ specificity) clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how indeterminate results were handled?	Quality Rating
Villarino, 2000[68]	Partially	Partially	Yes	Partially	NA	Yes	NA	Yes	Fair
Walsh, 2011[95]	Yes	NA	NA	Partially	NR	NR	No	Yes	Fair
Wang, 2013[131]	Yes	NA	NA	Yes	Yes	NR	Yes	No	Fair
Wang, 2015[253]	Partially	NA	Partially	Yes	No	NR	NA; raw data provided	Yes; indeterminate results were excluded, but <3% of cases	Poor
Wang, 2018[109]	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Good
Wang, 2018[254]	Yes	NA	Yes; not present	Yes	Yes	NR	NA; raw data provided	No; indeterminate results were excluded from the start, unclear how many	Fair
Warria, 2020[255]	Yes	NA	No; too high, 24.5% missing for TST	Yes	Yes	NR	NA; raw data provided	Unclear	Poor
Waruk, 2015[146]	Partially, Unclear timing of testing with respect to treatment	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR
Wawrocki, 2019[256]	Partially	Partially	Yes; not present	Partially	Yes	NR	NA; raw data provided	NR	Poor
Whitworth, 2012[150]	Partially	NA	NA	Yes	Yes	NR	Yes	Yes	Good
Whitworth, 2014[151]	Partially	Yes	NA	Yes	NA	NR	Yes	Yes	Fair

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

First Author, Year	Were selection criteria (for patients) clearly described?	Was the spectrum of patients included in the study representative of the patients who will receive the test in primary care?	Were withdrawals and missing data from the study adequately explained or not present?	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 (i.e., each test interpreted blinded to the result of the other)?	Were methods for calculating accuracy (e.g. sensitivity/ specificity) clearly reported and valid?	Did the study provide raw data on indeterminate results or enough information to understand how indeterminate results were handled?	Quality Rating
Whitworth, 2019[115]	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes	Fair
Wlodarczyk, 2014[77]	Partially	Partially	Yes	Yes	NA	NR	Yes	Yes	Good
Xu, 2017[257]	Yes	NA	Yes; not present	Yes	Yes	NR	NA; raw data provided	Yes; raw data	Fair
Xuan, 2017[105]	Partially	NA	Partially	Yes	Yes	NR	NA; raw data provided	Yes; indeterminate results were excluded, but <2% of cases	Fair for T.SPOT.*TB* Poor for TST
Yi, 2016[122]	Yes	Yes	Yes; adequately explained	Yes	Yes	NR	Yes	Yes; indeterminate results were excluded, but only 3% of cases	Fair; blinding NR
Yu, 2015[83]	Yes	NA	Yes; not present	Yes	Yes	Yes	NA; raw data provided	NA	Good
Zhang, 2017[108]	Yes	NA	Yes; adequately explained	Yes	Yes	Yes	NA; raw data provided	Yes, indeterminate results were excluded, but only 5.2% of cases	Good
Zhu, 2019[82]	Partially	NA	Yes	Yes	Yes	NR	NA	Yes	Fair; blinding NR

Abbreviations: ATB=active tuberculosis; HCW=healthcare worker; KQ=key question; NA=not available; NR=not reported; QFT=QuantiFERON-TB; QFT-G=QuantiFERON TB Gold® test (2nd generation test); QFT-GIT=QuantiFERON-TB Gold-In-Tube® test (3rd-generation test); Sp=specificity; Sn=sensitivity; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test; vs.=versus.

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

First 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?
Denholm, 2017[258] SIRCLE 80	Yes	Unclear	Partially; authors did not do the statistical comparison but a few characteristics look different (female, ALT, region, and immunosuppression)	Likely; suggest that 85% 9H group and 90% 3HP group "completed therapy"; however, the mean time to discontinuation is relatively short compared with the treatment duration	Did not complete: 10 (12.5)	Did not complete: 9H: 6 (15%) 3HP: 4 (10%) Differential attrition rate: 5%
Gao, 2018[181] 3,738	Yes (detail in supplement)	Yes	Yes, for most characteristics (although, statistically significant difference for pulmonary fibrotic lesions, small magnitude, of unclear clinical significance)	Probably yes (85% completed the modified regimen A); although high frequency of adverse effects limited completion of LTBI regimens for many	Unclear for 2-year outcomes (NR in study flow diagram); for short term harms data, they report 2.6% (33/1284) unreachable in Group A and 3.9% (51/1,299) unreachable in Group B.	Unclear for 2-year outcomes
Menzies, 2004[177] 116	Yes	Partially	Yes	Yes, RIF: 53 (91) took 80% of doses, 50 (86) took more than 90% of doses within 20 weeks INH: 44 (76) took 80% of doses; 36 (62) took 90% doses for 43 weeks 80% 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)

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

First 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?
Menzies, 2008[160] 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%)

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

First 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?
Menzies, 2018[161] 6,012	Yes	Unclear	Yes	Partially INH: 1,890 (63.2) took 80% of doses, 1,099 (36.8) took <80% of doses RIF: 2,382 (78.8) took 80% of doses, 641 (21.2) took <80% of doses	Treatment not completed for any reason: 1,740 (28.9) Death during treatment: 3 (0.1) Diagnosis of active TB: 2 (<0.1) Treatment stopped permanently for Grade 1–4 event: 211 (3.5) Treatment started, but participant decided to stop: 1,208 (20.1)	Treatment not completed for any reason: INH: 1,099 (36.8) RIF: 641 (21.2) Differential: 15.6 Death during treatment: INH: 3 (0.1) RIF: 0 (0) Differential: 0.1 Diagnosis of active TB: INH: 1 (<0.1) RIF: 1 (<0.1) Differential: 0 Treatment stopped permanently for Grade 1–4 event: INH: 143 (4.8) RIF: 68 (2.2) Differential: 2.6 Treatment started, but participant decided to stop: INH: 772 (25.8) RIF:436 (14.4) Differential: 11.4
Sterling, 2011[162,*] PREVENT TB 6,886	Partially	NR	Yes	Yes	Treatment completion:* 2,895 (80.8%) 2,264 (68.2%)	Differential treatment completion:* 12.6%

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

First 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?
Sterling, 2015[179] PREVENT TB 7,552	Yes	Yes	Yes	Yes Overall: 75.8% 9H: 69.0% 1,160 did not complete regimen/3,745 eligible for MITT 3HP: 82.2% 713 did not complete regimen/3,986 eligible for MITT	Did not complete 33 months of followup: 1,008 (13.0%)	Differential attrition: 2% Did not complete 33 months of followup: 9H: 450 (12.0%) 3HP: 558 (14.0%)
Sun, 2018[163] 263	Yes	Yes	Yes	Yes Poor adherence: 3HP: 0 (0) 9H: 16 (12.2)	Noncompletion: 33 (12.5) Adverse drug reactions: 19 (7.2) Consent withdrawal: 24 (9.1)	Noncompletion: 3HP: 14 (10.6) 9H: 29 (22.1) Differential: 11.5 Adverse drug reactions: 3HP: 12 (9.1) 9H: 7 (5.3) Differential: 3.8 Consent withdrawal: 3HP: 2 (1.5) 9H: 22 (16.8) Differential: 15.3
Surey, 2021[180] HALT LTBI pilot study 52	Yes	Unclear	Partially Groups looked mostly similar but no formal statistical comparison. Authors say “no evidence of major imbalance.”	Yes; 76.9% received at least 90% of prescribed doses	Failed to complete trial: 12 (23.1)	Failed to complete trial: 3HP: 6 (22.2) 3HR: 6 (24)

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

First 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?
Thompson, 1982[159] IUAT 27,830	Yes	Yes	Unclear	Yes	5-year followup not complete for 781 (2.8%)	<5%
White, 2012[178] 364	Yes	Partially	Yes	No; nearly 1/2 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)

Abbreviations: 3HP=rifapentine plus INH; 3HP=3 months of weekly INH and RIF; 9H=9 months of daily directly observed INH alone; AE=adverse event; ALT=alanine aminotransferase ; CI=confidence interval; INH=isoniazid; IUAT=International Union Against Tuberculosis; KQ=key question; LTBI=latent tuberculosis infection; MITT=modified intention to treat ; NR=not reported; RIF=rifampin; RR=relative risk; SIRCLE=short-court isoniazid and rifapentine for cost-effective latent tuberculosis eradication trial; TB=tuberculosis.

Appendix E Table 3. Quality Ratings for Randomized, Controlled Trials (KQs 3 and 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
Denholm, 2017[258] SIRCLE 80	Unclear	No	No	No	Unclear	Unclear	Unclear	Unclear	Poor	Lack of masking; unclear allocation concealment; focus of study is on cost analysis and not on our outcomes of interest; unclear outcome ascertainment methods (not described)
Gao, 2018[181] 3,738	Yes	No (open label)	No	Yes (expert panel was blinded to treatment assignment)	Yes	Unclear	Yes (and had a per-protocol analysis)	Yes	Fair	Open label; study planned for 3-month regimen but shortened it because of adverse effects
Menzies, 2004[177] 116	Yes	No	No	No	No	Yes	Yes	Yes	Fair	Open label; authors stated unblinded study justified because the primary study outcome, treatment completion, was likely strongly influenced by duration of therapy Primary outcome % 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)

Appendix E Table 3. Quality Ratings for Randomized, Controlled Trials (KQs 3 and 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
Menzies, 2008[160] 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
Menzies, 2018[161] 6,012	Yes	No	No	Partially	Yes	Unclear	Yes	Yes	Fair	Note: This study included data from the Phase 2 and Phase 3 trials, some from ineligible countries
Sterling, 2011[162] PREVENT TB 6,886	Yes	NR	NR	NR	Yes	Yes	Yes	Yes	Fair	Masking unclear and higher overall attrition
Sterling, 2015[179] PREVENT TB 7,552	Yes	No	No	No	Yes	Unclear	Yes (based on previous study)	Yes	Fair	Used an older paper from this trial for much of this information
Sun, 2018[163] 263	Yes	No	No	No	Yes	Unclear	Yes	Yes	Fair	Differential attrition, mostly due to poor adherence but likely a product of the different length of treatments
Surey, 2021[180] HALT LTBI pilot study 52	Yes	No	No	No	Yes	Unclear	No	Partially	Fair	Some lack of information on the analysis
Thompson, 1982[159] IUAT 27,830	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good (for KQ 3) Fair (for KQ 5)	

Appendix E Table 3. Quality Ratings for Randomized, Controlled Trials (KQs 3 and 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
White, 2012[178] 364	Yes	No	No	No	No	Yes	Yes	Yes	Fair	Open label; nearly half 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; IUAT=International Union Against Tuberculosis; KQ=key question; LTBI=latent tuberculosis infection; NR=not reported; RIF=rifampin; SIRCLE=short-court isoniazid and rifapentine for cost-effective latent tuberculosis eradication trial; TB=tuberculosis.

Appendix E. Table 4. Quality Assessment of Systematic Reviews, Network Meta-Analyses, and IPD Meta-Analyses (KQs 3, 5)

First Author, Year	Were the study eligibility criteria adequate?	Were the methods of study identification and selection adequate?	Was data collection adequate?	Were the synthesis methods adequate?	Quality Rating
Zenner, 2017[164]	Yes	Yes	Yes	Yes	Good

Abbreviations: IPD=individual patient data; KQ=key question.

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

First 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
Denholm, 2017[258] SIRCLE 80	Unclear	No	Unclear	Yes	Poor	Lack of masking; unclear allocation concealment; focus of study was on cost analysis and not on the outcomes of interest; unclear outcome ascertainment methods (not described); insufficient description of analysis
Gao, 2018[181] 3,738	Yes	Yes	Yes	Yes	Fair	Open label; study planned for 3-month regimen but shortened it because of adverse effects
Menzies, 2004[177] 116	Yes	Yes	Partially	No	Fair	Followup likely insufficient; some AEs subject to judgment of severity (e.g., fatigue, nausea)
Menzies, 2008[160] 847	Yes	Yes	Yes	Yes	Good	
Menzies, 2018[161] 6,012	yes	Yes	Yes	Yes	Fair	Open label; unclear allocation concealment
Sterling, 2011[162] PREVENT TB 6,886	Yes	Yes	Yes	Yes	Fair	
Sterling, 2015[179] PREVENT TB 7,552	yes	Yes	Unclear	Yes	Fair	Open label; used Naranjo scale (but modified it), defined what is considered severe; unclear if ascertainment techniques were equal across study arms because classification of whether adverse effects were attributed to medications was determined by local prescribing physicians

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

First 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
Sun, 2018[163] 263	Yes	Yes	Yes, valid and reliable; not equal because monitoring certain blood tests for adverse effects was during treatment (and treatment duration differed for the groups, 3 months vs. 9 months)	Adequate during treatment, but no post-treatment assessment described	Fair	Open label; used Naranjo scale with defined cutoffs; also defined clinically relevant hepatic elevations
Surey, 2021[180] 52	Yes	Yes	Yes	Yes	Fair	Open label; unclear if ascertainment techniques were equal across study arms because classification of whether adverse effects were related to study regimen was determined by prescribing physicians

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

First 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
Thompson, 1982[159] 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[178] 364	Yes	Yes	Yes	No	Fair	Nearly one half of participants who started were lost to followup by transfer to another facility or deportation, thus unable to adequately track harms

Abbreviations: AE=adverse event; INH=isoniazid; IUAT=International Union Against Tuberculosis; KQ=key question; NR=not reported; TB=tuberculosis.

Appendix E Table 6. Quality Ratings for Observational Studies for Harms (KQ 5): Main Analysis, Part 1

Author, Year Trial Name N	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 differential attrition?	Did the study have a high attrition raising concern for bias?
Schein, 2018[259]	Partially	No	NR	Yes	Yes	Yes	NR	No	0	No

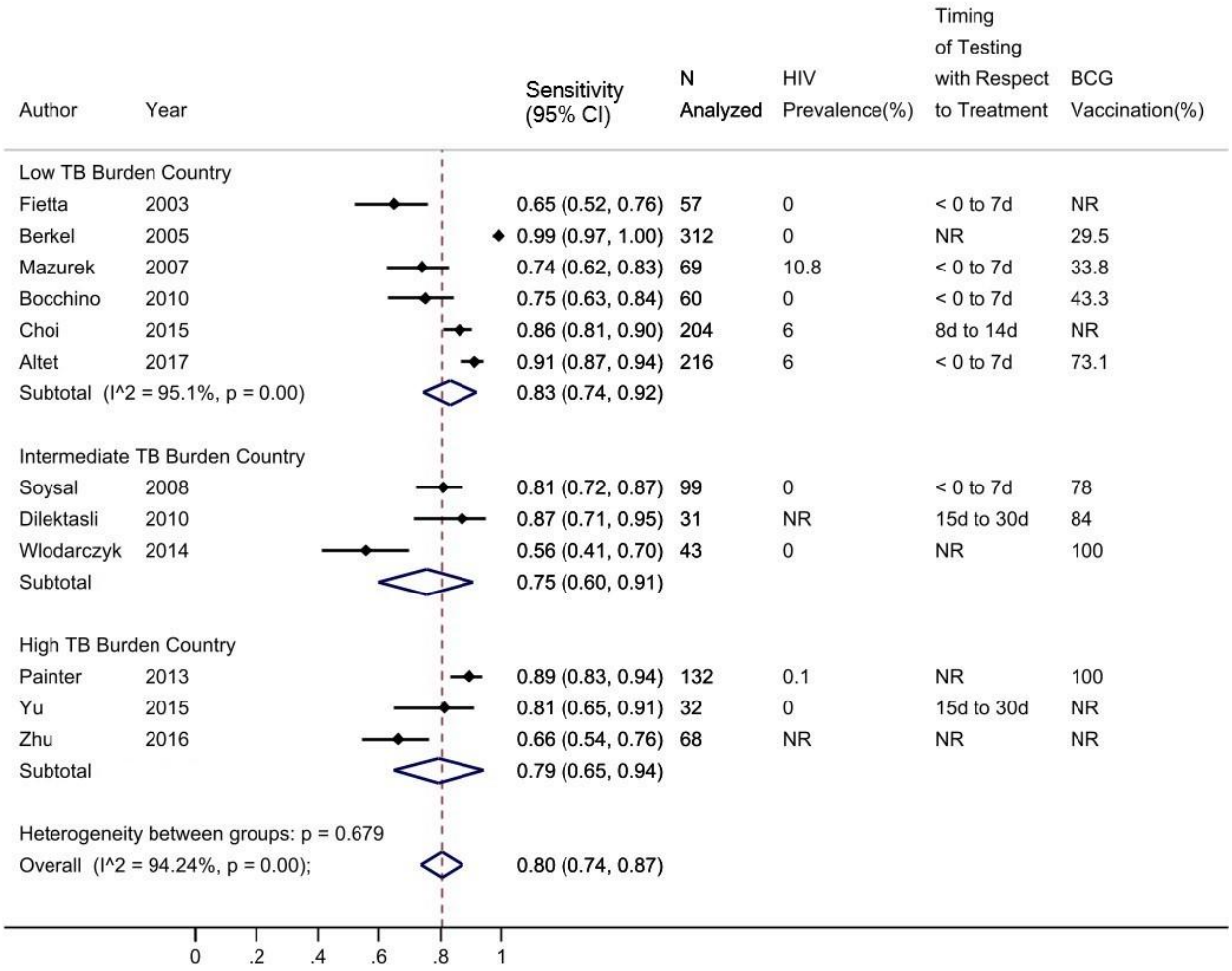
Abbreviations: KQ=key question; N=number; NR=not reported.

Appendix E Table 7. Quality Ratings for Observational Studies for Harms (KQ 5): Main Analysis, Part 2

Author, Year Trial Name N	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
Schein, 2018[259]	NR	No	NR	Yes	No	No	Yes	Yes	Poor	Unclear inclusion criteria; no masking of outcomes assessors; unclear process of collection of harms data; partial harms data reported only (only if it led to treatment interruption or termination)

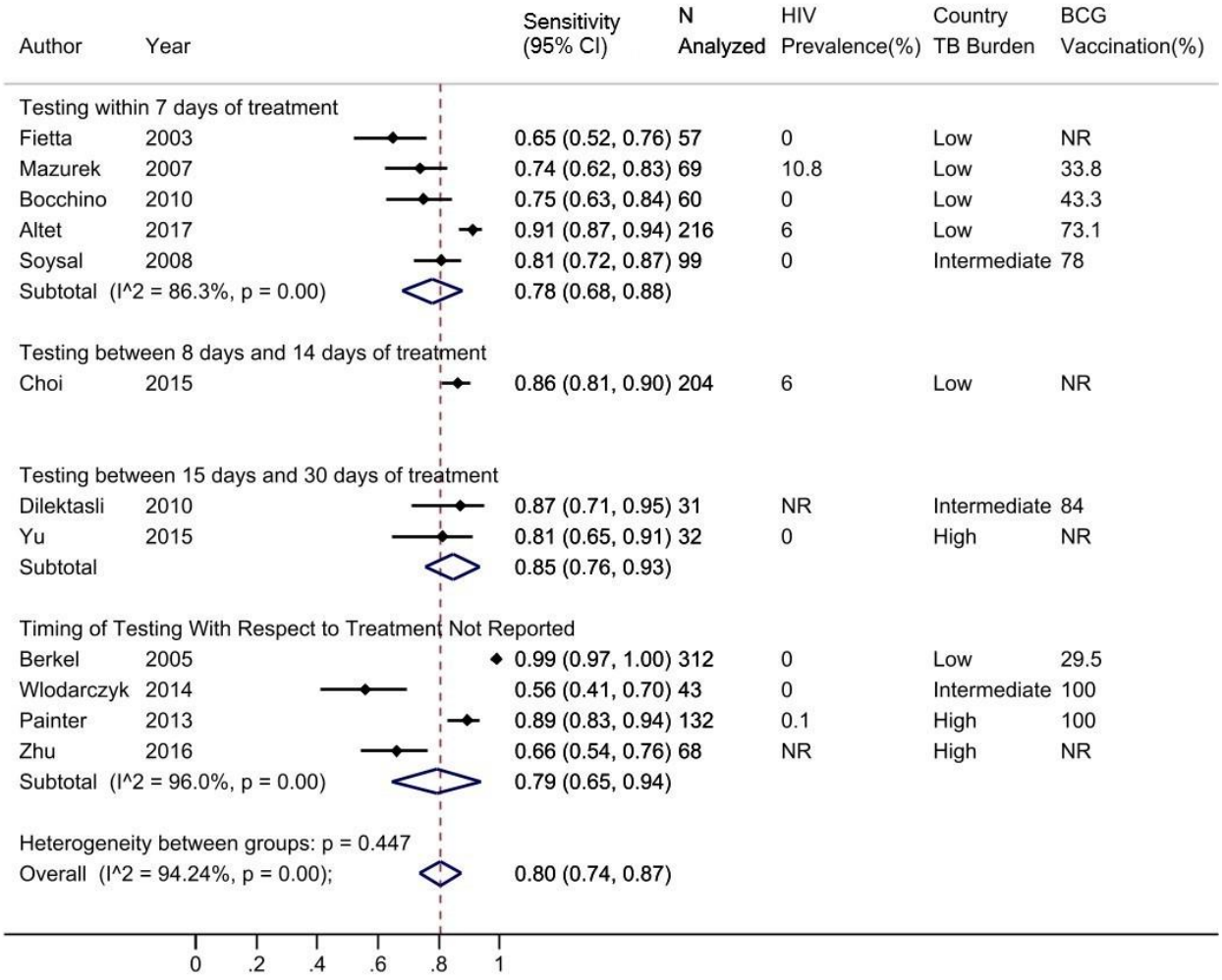
Abbreviations: KQ=key question; N=number; NR=not reported.

Appendix F Figure 1. Sensitivity for TST at 5-mm Threshold, Stratified by Country TB Burden of the Study Setting



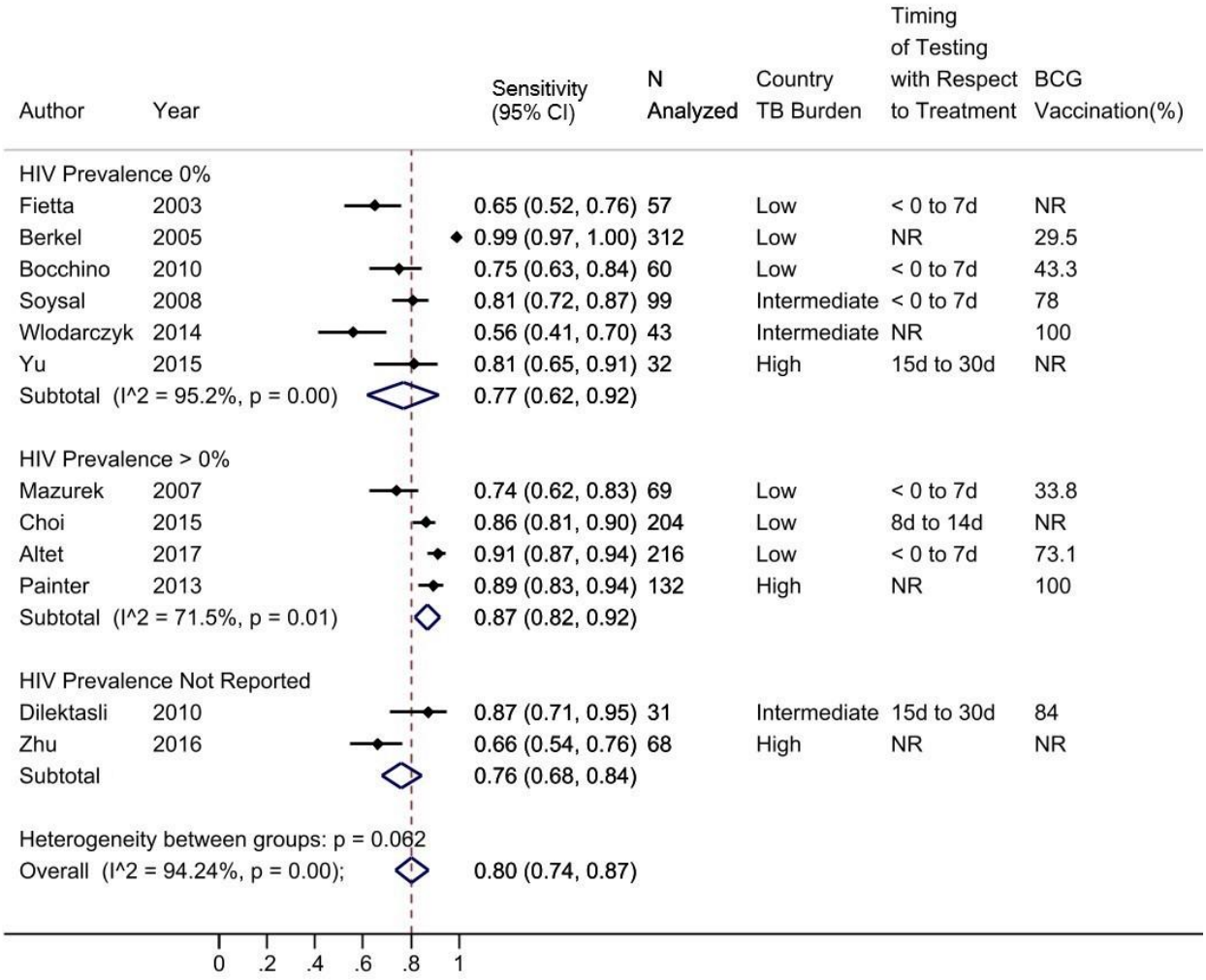
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 2. Sensitivity for TST at 5-mm Threshold, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



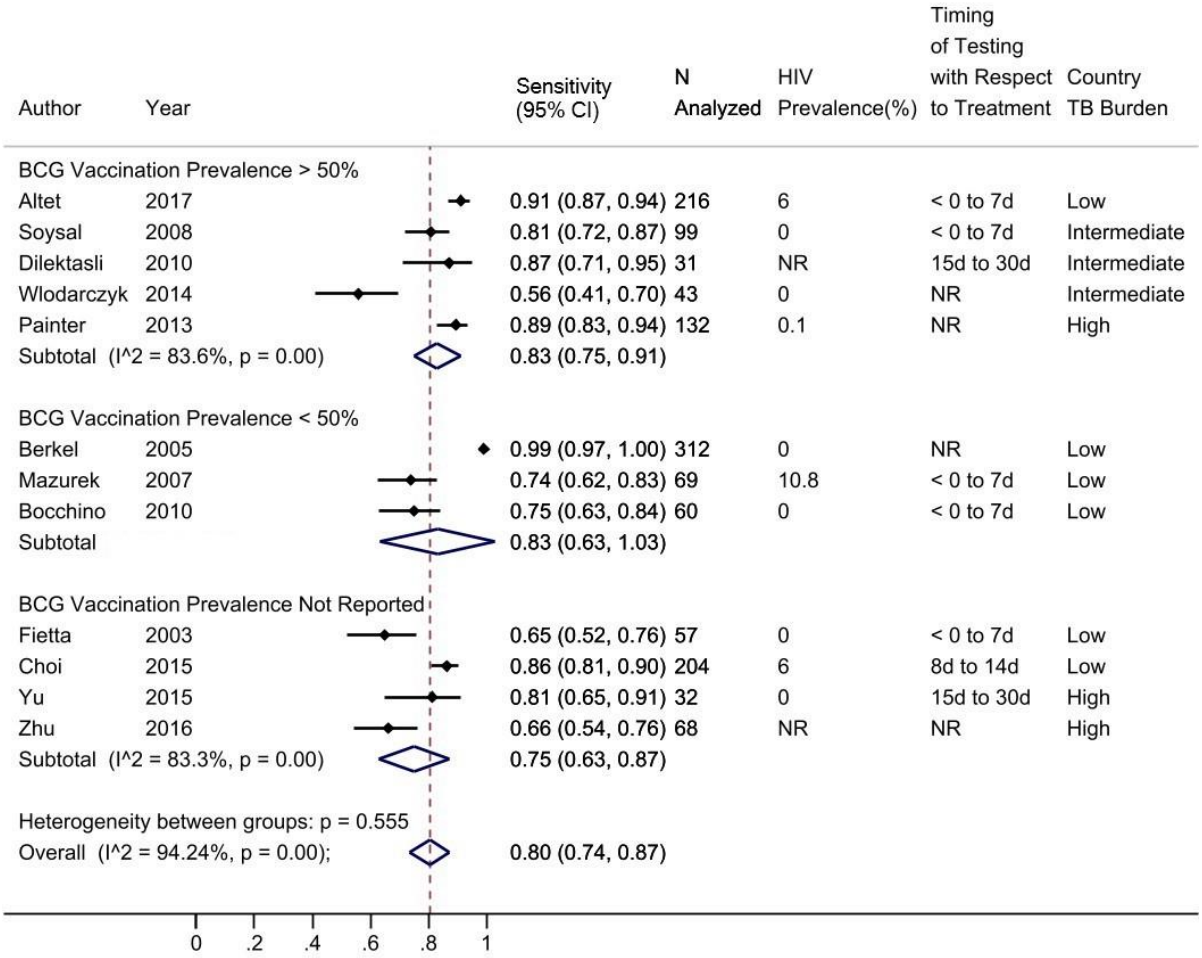
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 3. Sensitivity for TST at 5-mm Threshold, Stratified by HIV Prevalence of the Study Population



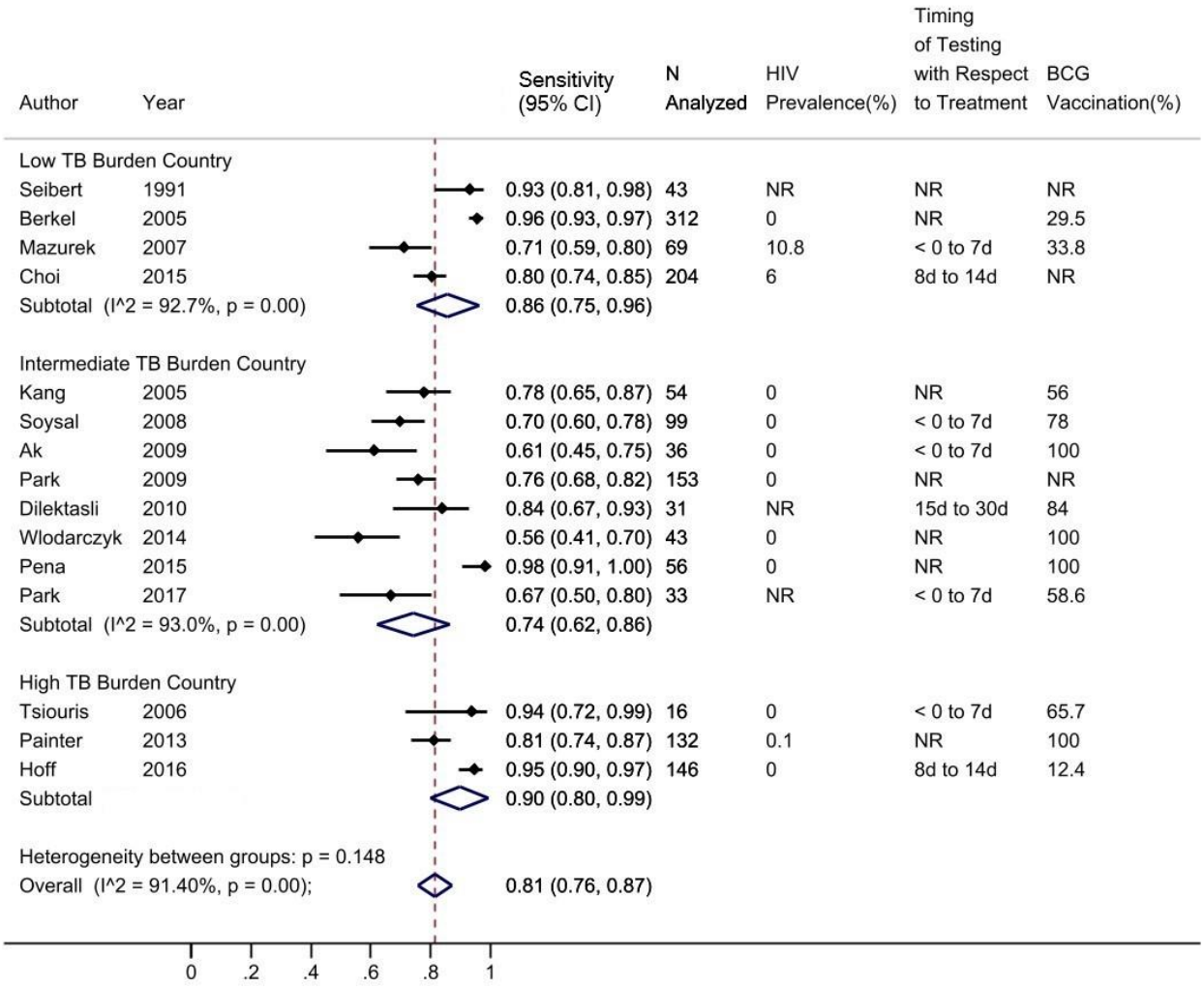
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 4. Sensitivity for TST at 5-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Setting



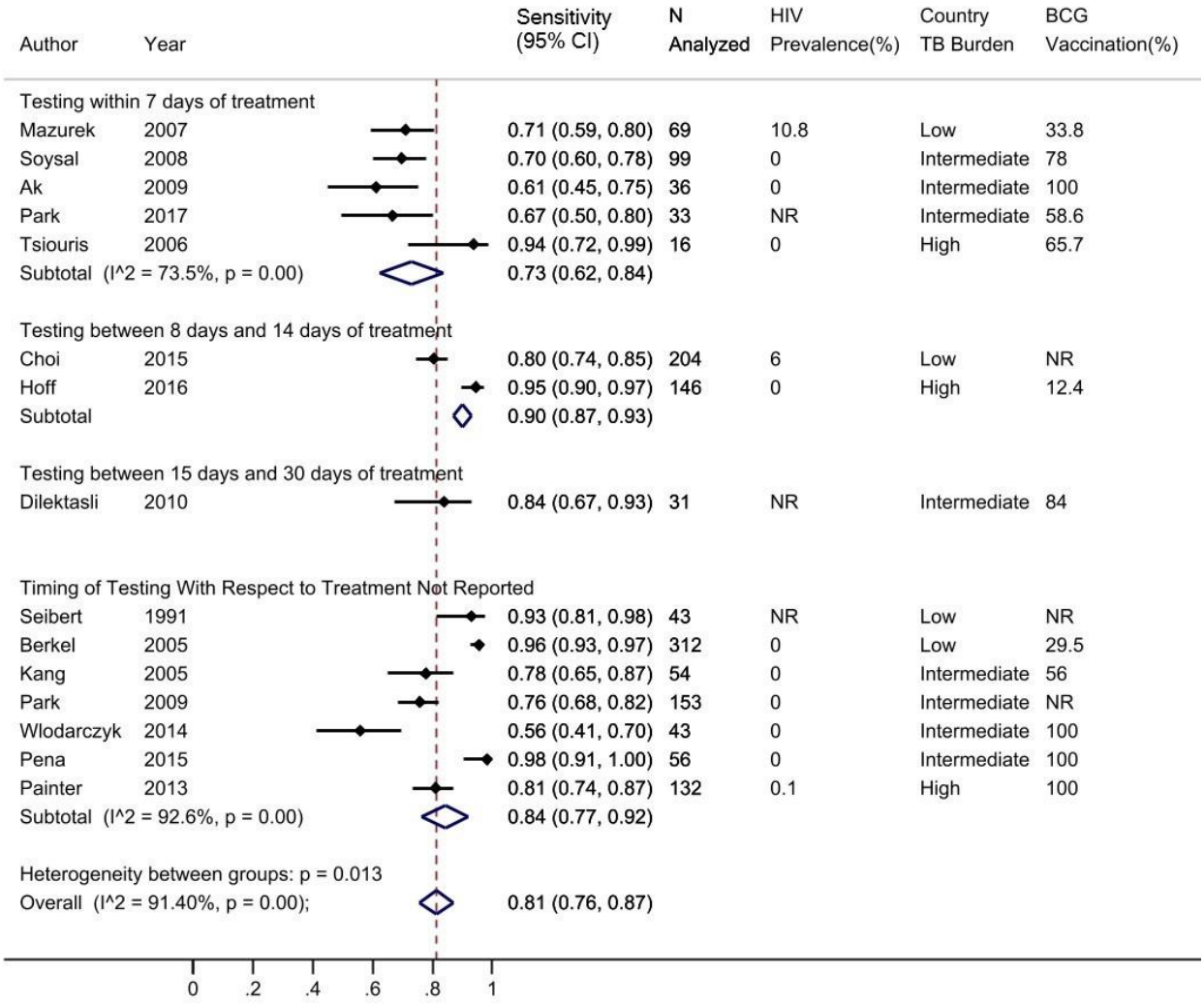
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 5. Sensitivity for TST at 10-mm Threshold, Stratified by Country TB Burden of the Study Setting



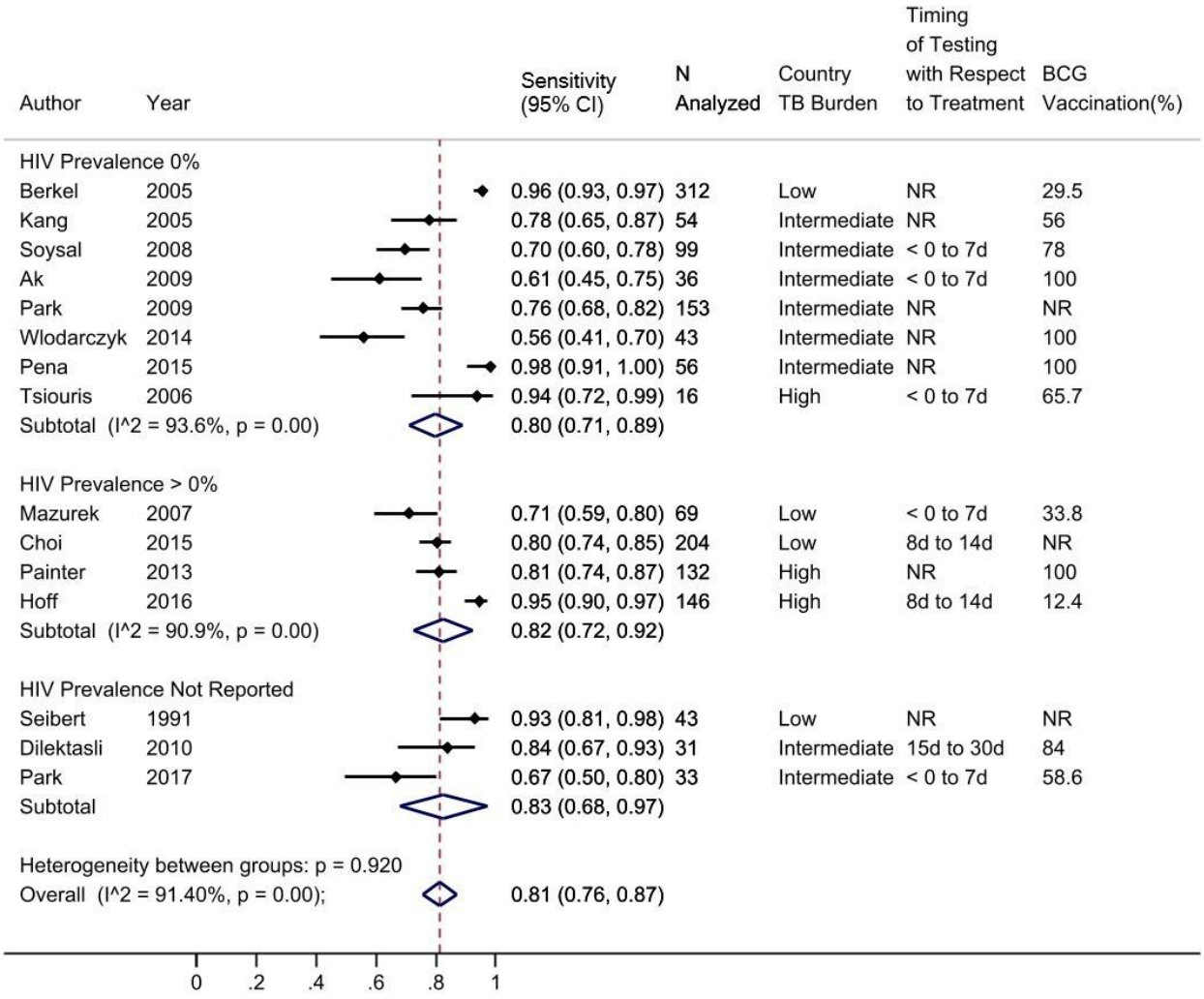
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 6. Sensitivity for TST at 10-mm Threshold, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



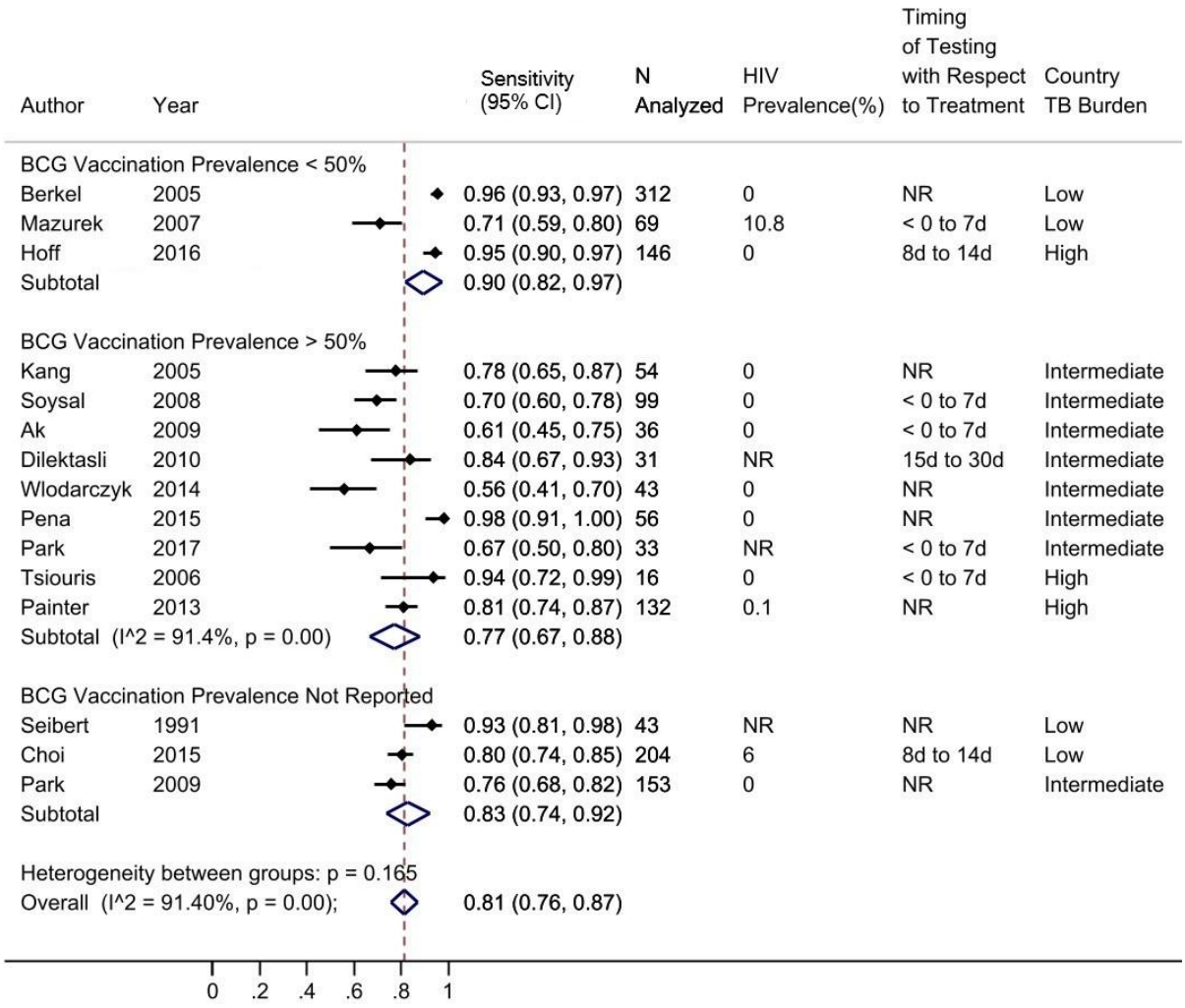
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 7. Sensitivity for TST at 10-mm Threshold, Stratified by HIV Prevalence of the Study Population



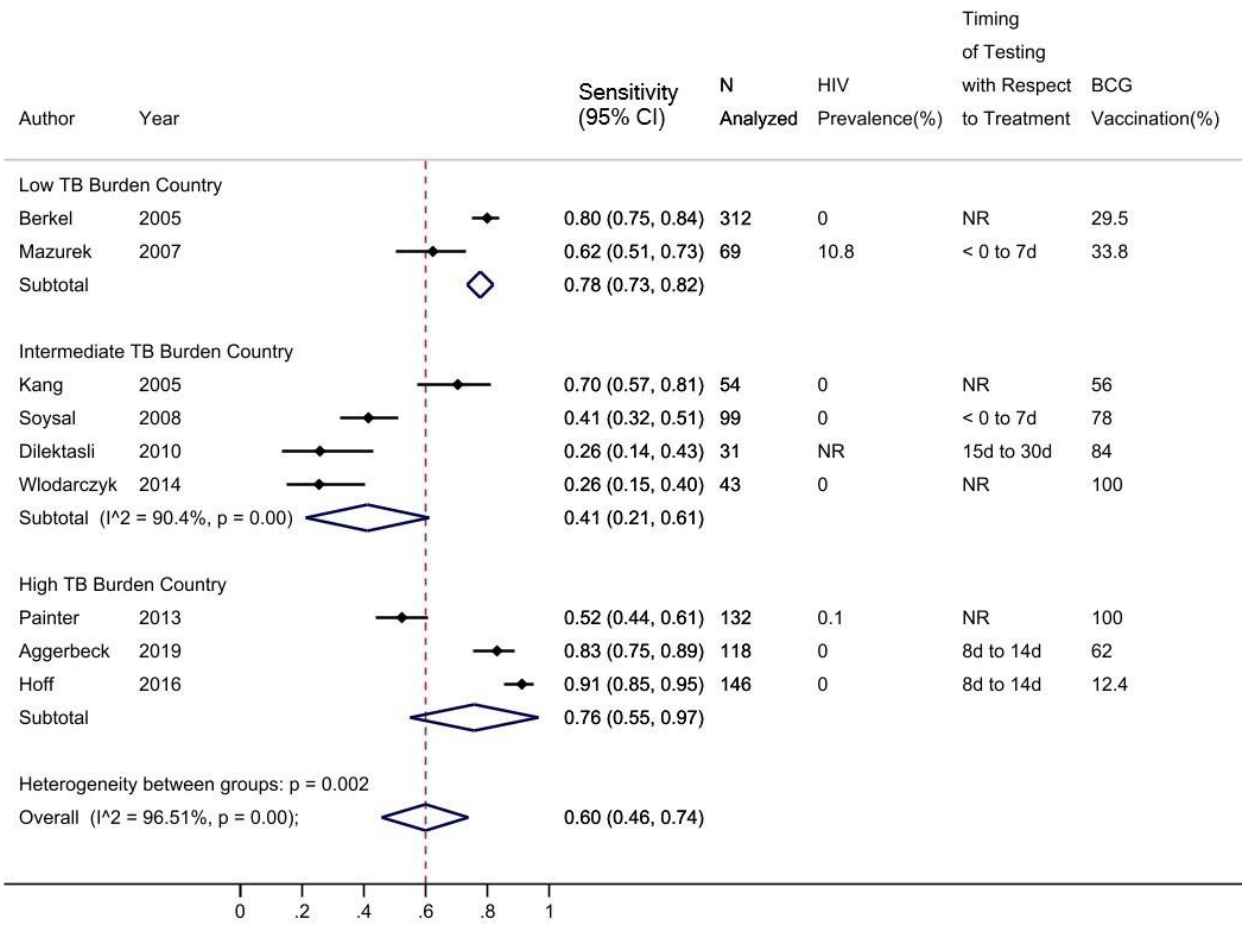
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 8. Sensitivity for TST at 10-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Setting



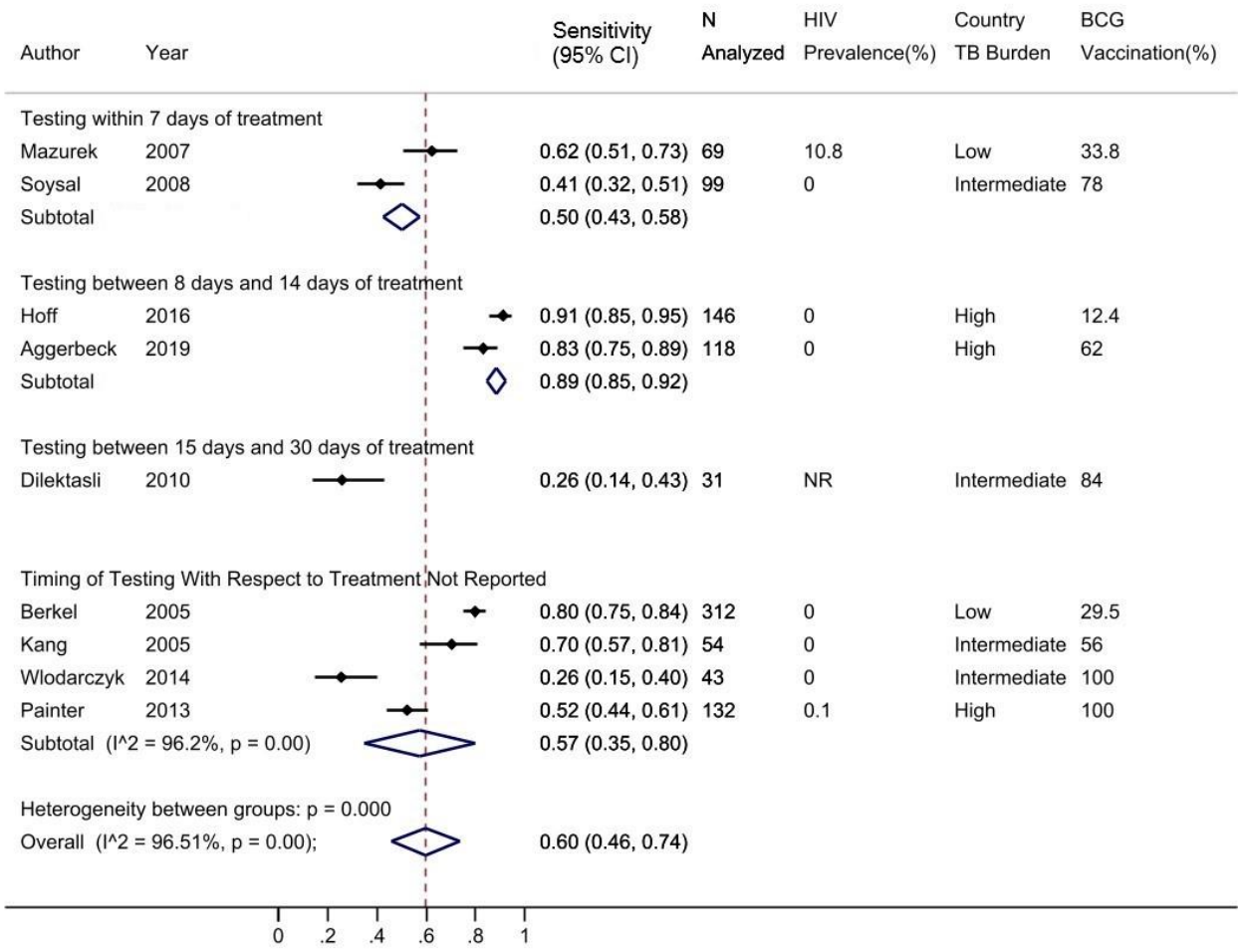
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 9. Sensitivity for TST at 15-mm Threshold, Stratified by Country TB Burden of the Study Setting



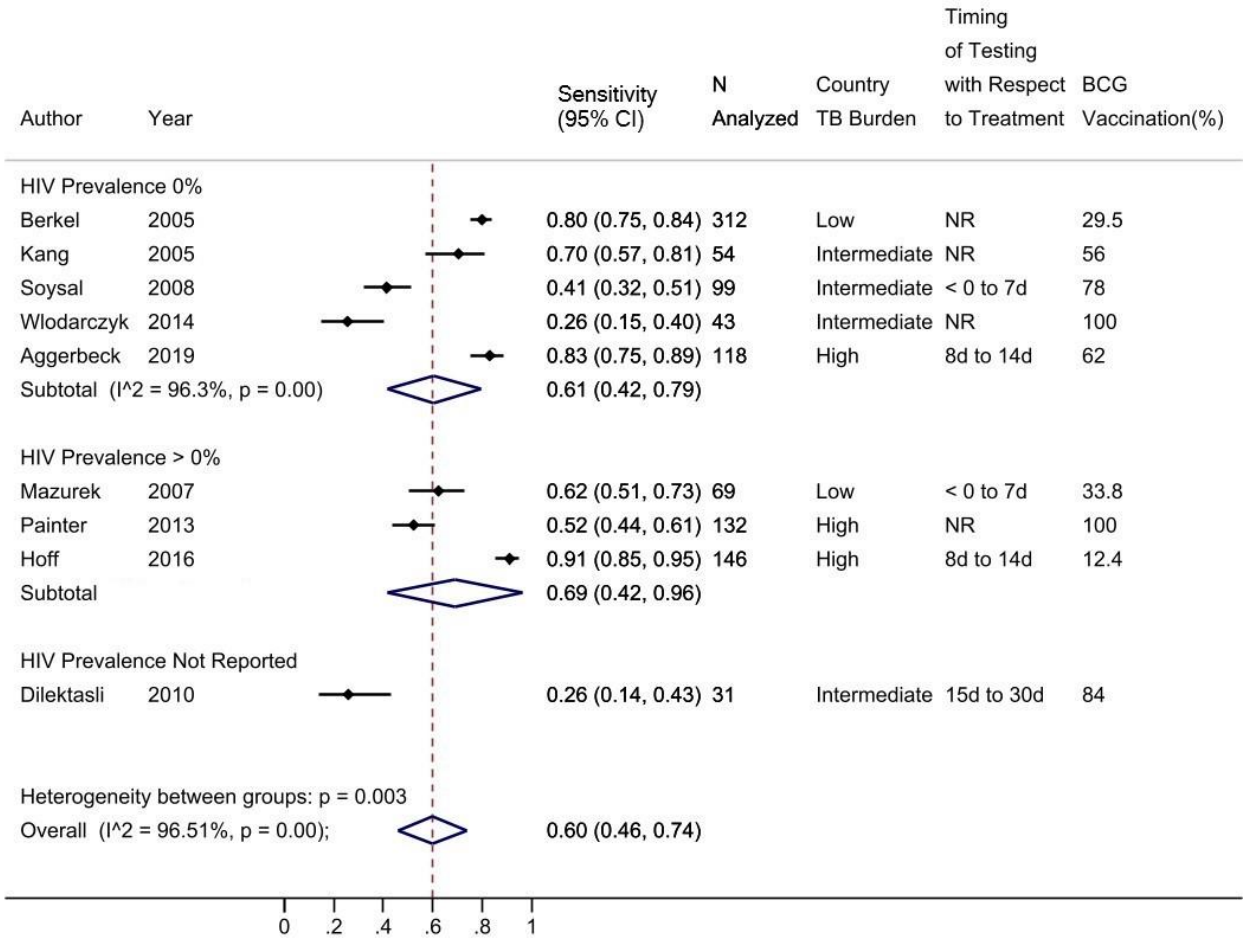
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 10. Sensitivity for TST at 15-mm Threshold, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



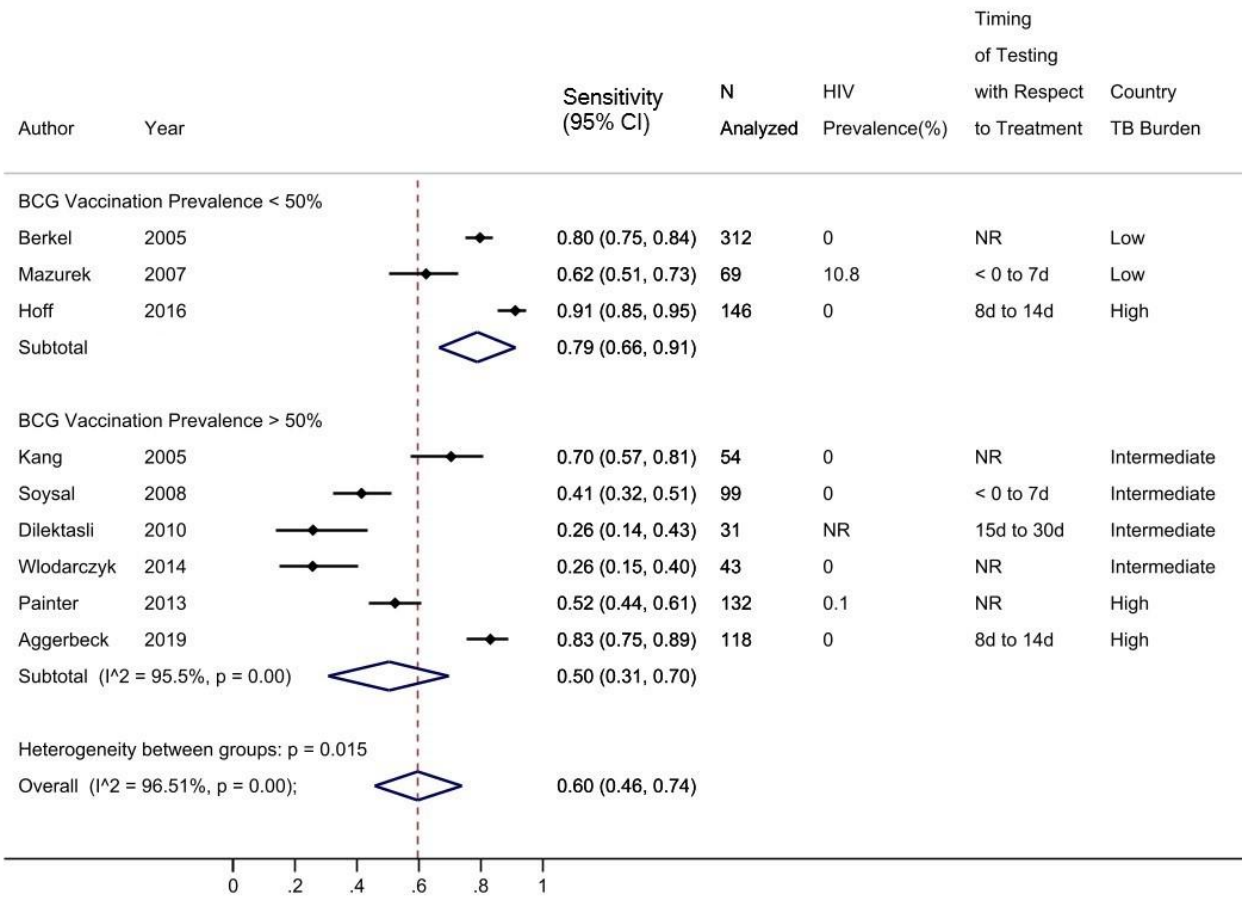
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 11. Sensitivity for TST at 15-mm Threshold, Stratified by HIV Prevalence of the Study Population



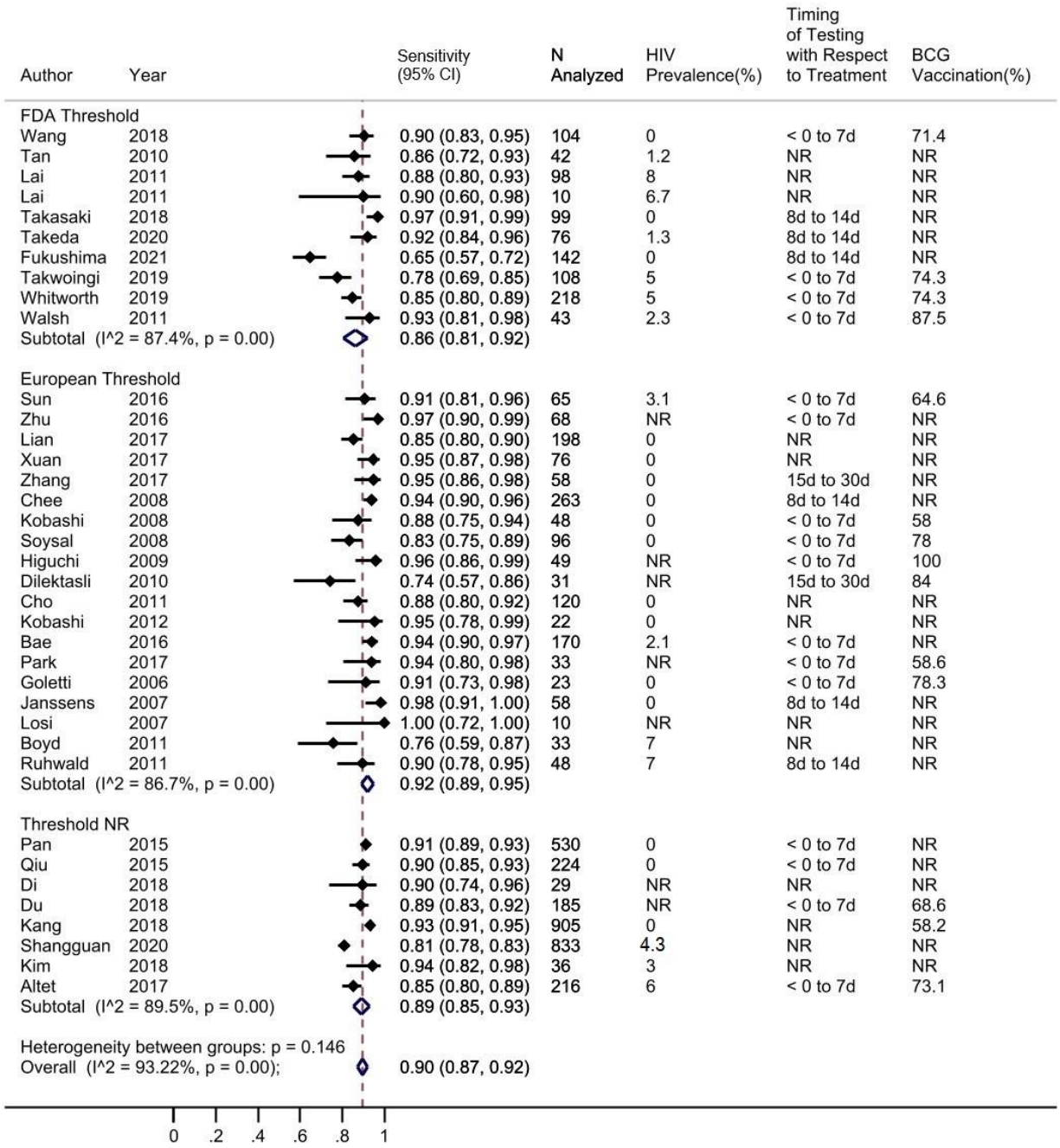
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 12. Sensitivity for TST at 15-mm Threshold, Stratified by BCG Vaccination Prevalence of the Study Setting



Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; TST=tuberculin skin test.

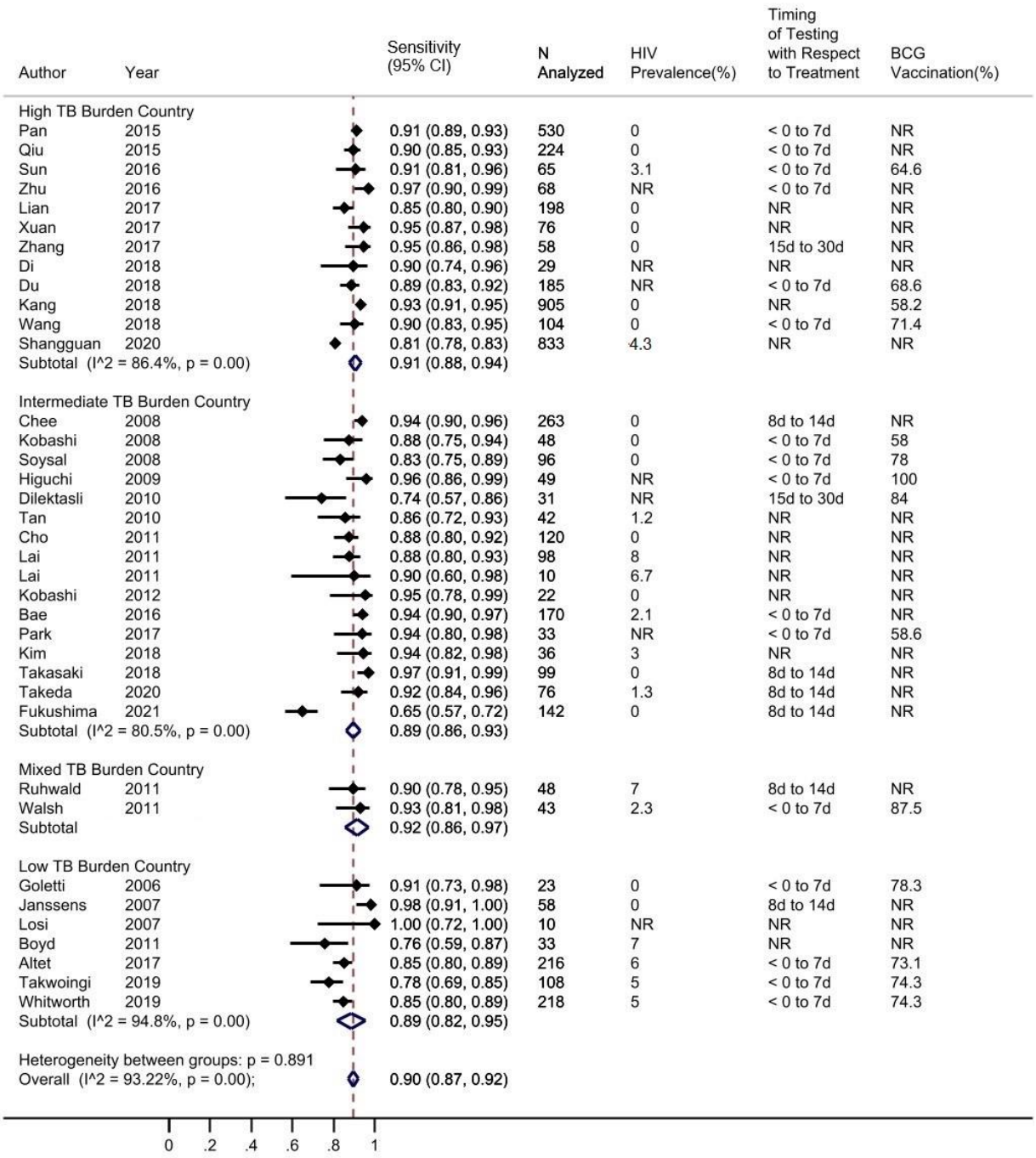
Appendix F Figure 13. Sensitivity for T-SPOT.*TB* Test, Stratified by Threshold Used for Positive Test



Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

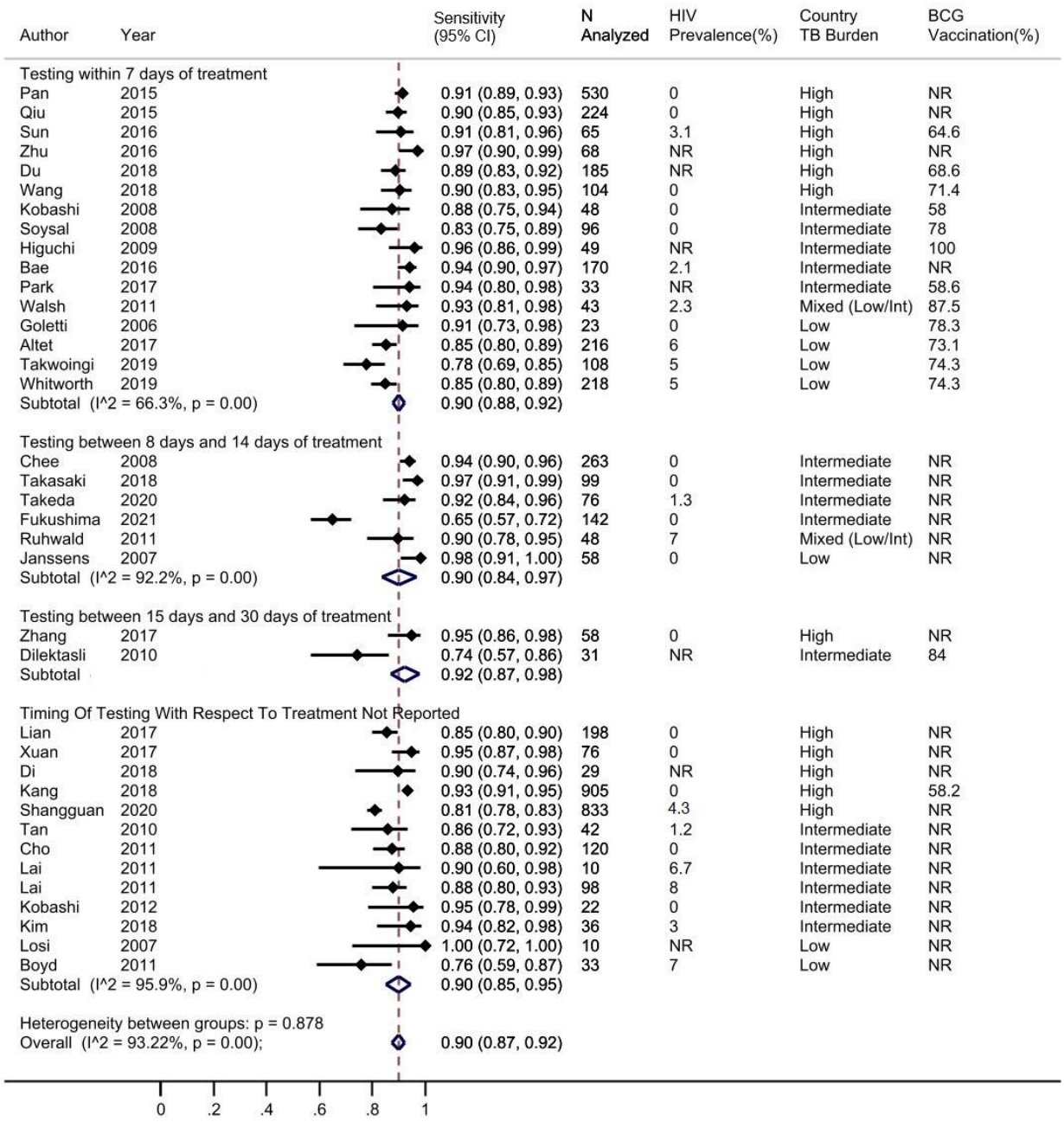
Figure Note: The FDA-approved labeling uses a threshold of 8 or more spots for a positive test and 4 or fewer spots for a negative test (unless the total number of spots is less than 20); 5, 6 or 7 spots are considered borderline or equivocal. The labeling approved for use in European and other countries uses a threshold of 6 or more spots for a positive test and a negative test is 5 or fewer spots.

Appendix F Figure 14. Sensitivity for T-SPOT.*TB* Test, Stratified by Country TB Burden of the Study Setting



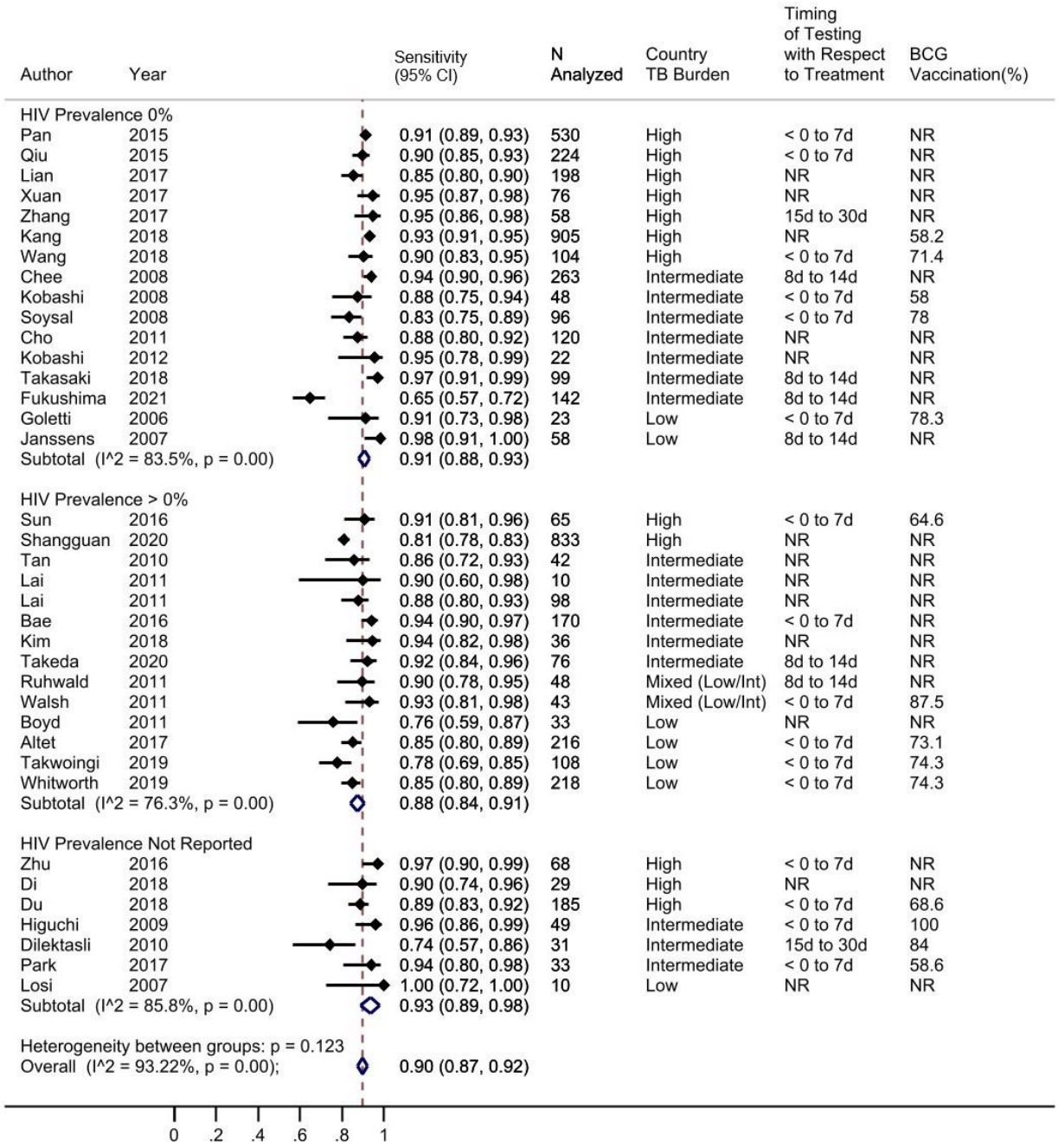
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

Appendix F Figure 15. Sensitivity for T-SPOT.*TB* Test, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



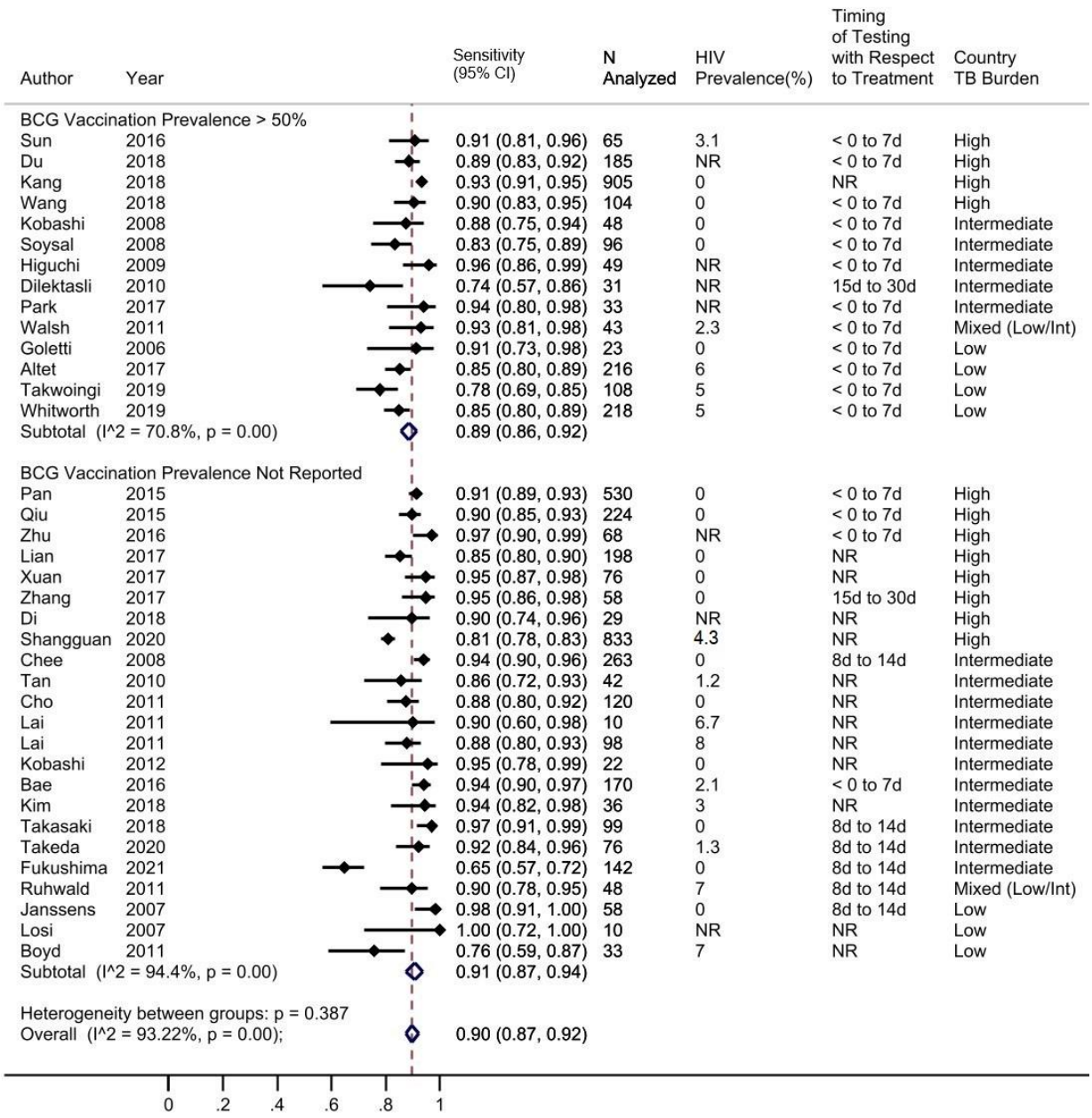
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

Appendix F Figure 16. Sensitivity for T-SPOT.*TB* Test, Stratified by HIV Prevalence of the Study Population



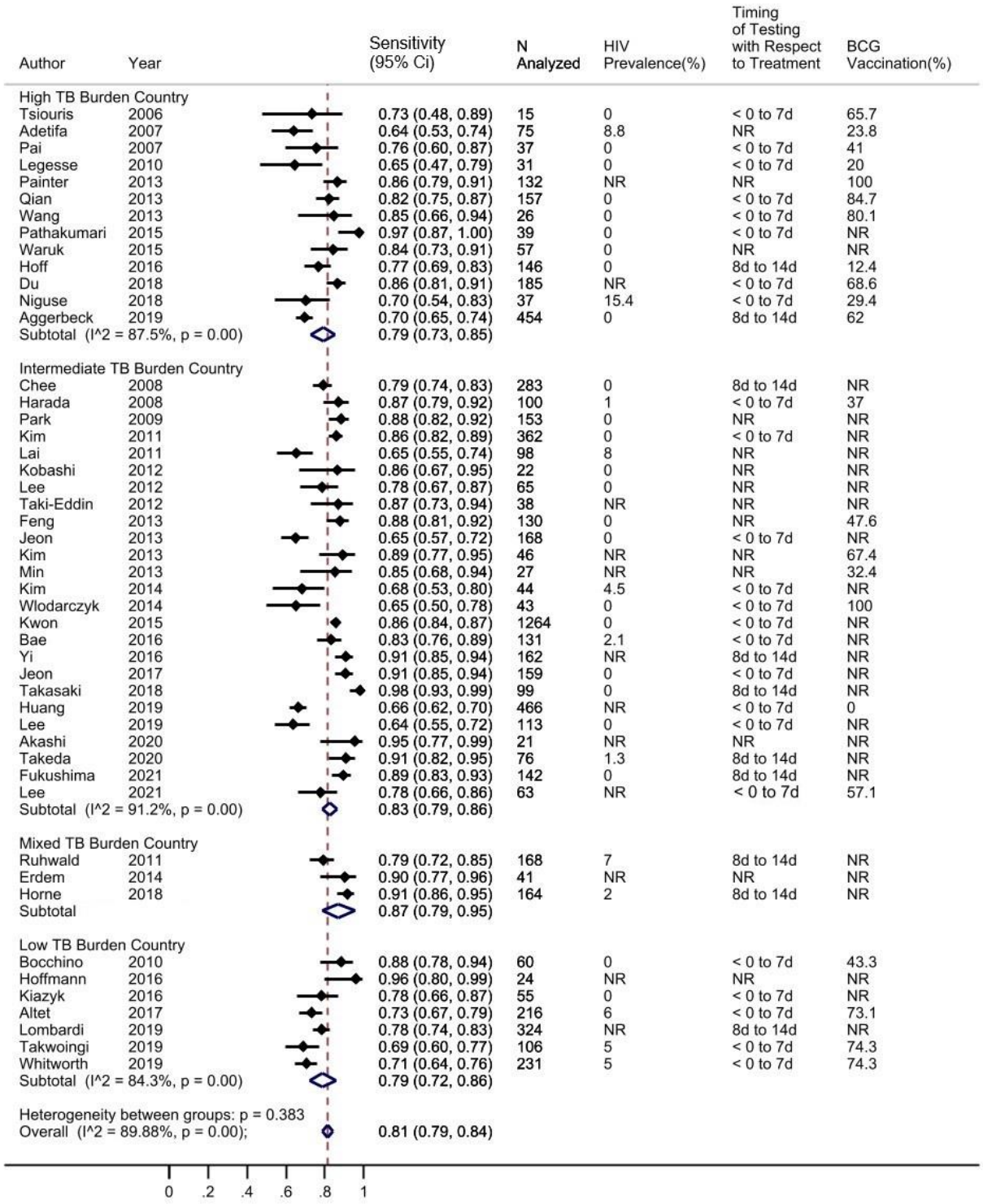
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

Appendix F Figure 17. Sensitivity for T-SPOT.*TB* Test, Stratified by BCG Vaccination Prevalence of the Study Setting



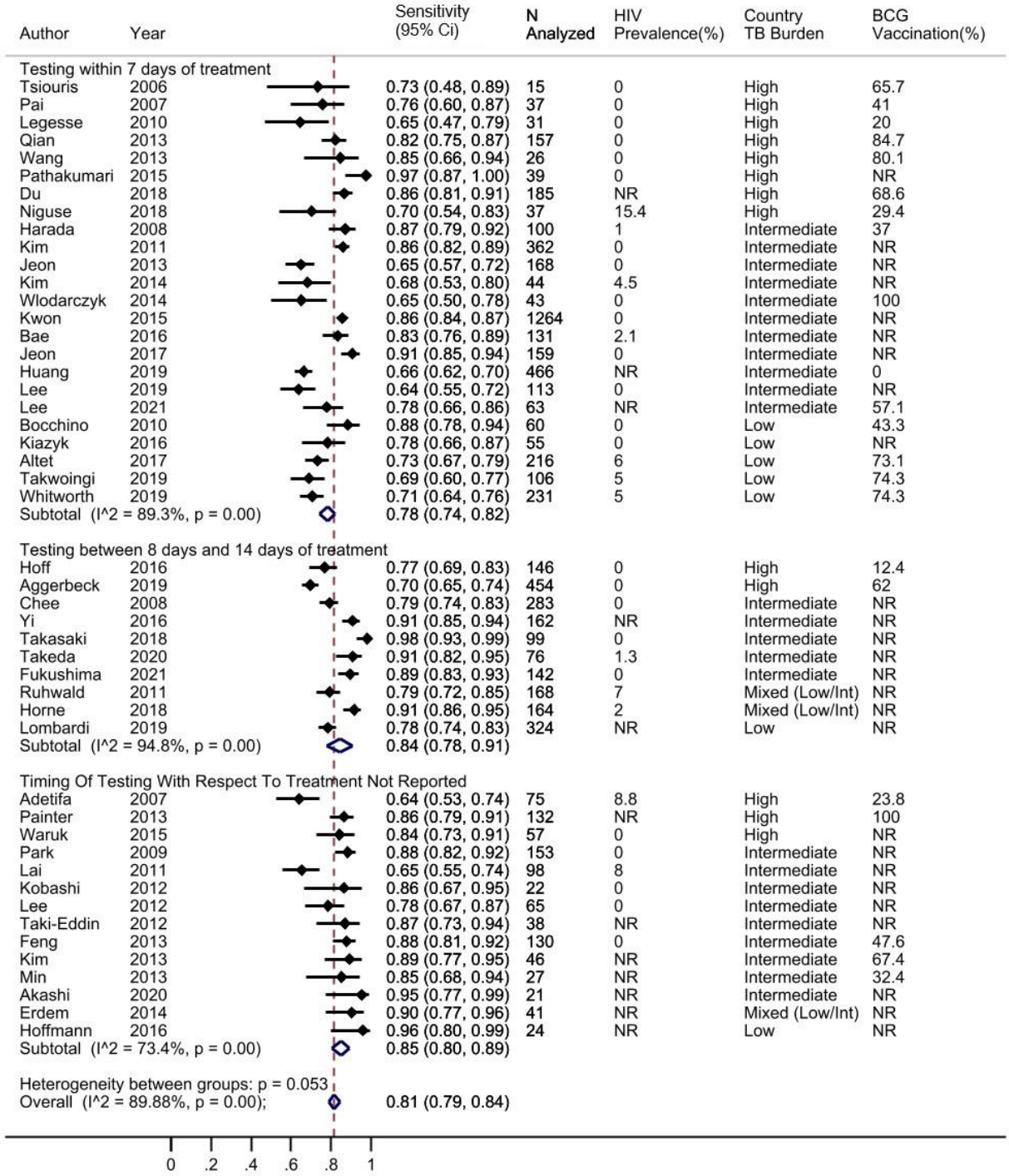
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; Int=intermediate; N=number; NR=not reported; TB=tuberculosis; T-SPOT.*TB*=commercial ELISPOT assay; TST=tuberculin skin test.

Appendix F Figure 18. Sensitivity for QFT-Gold In-Tube (3rd Generation) Test, Stratified by Country TB Burden of the Study Setting



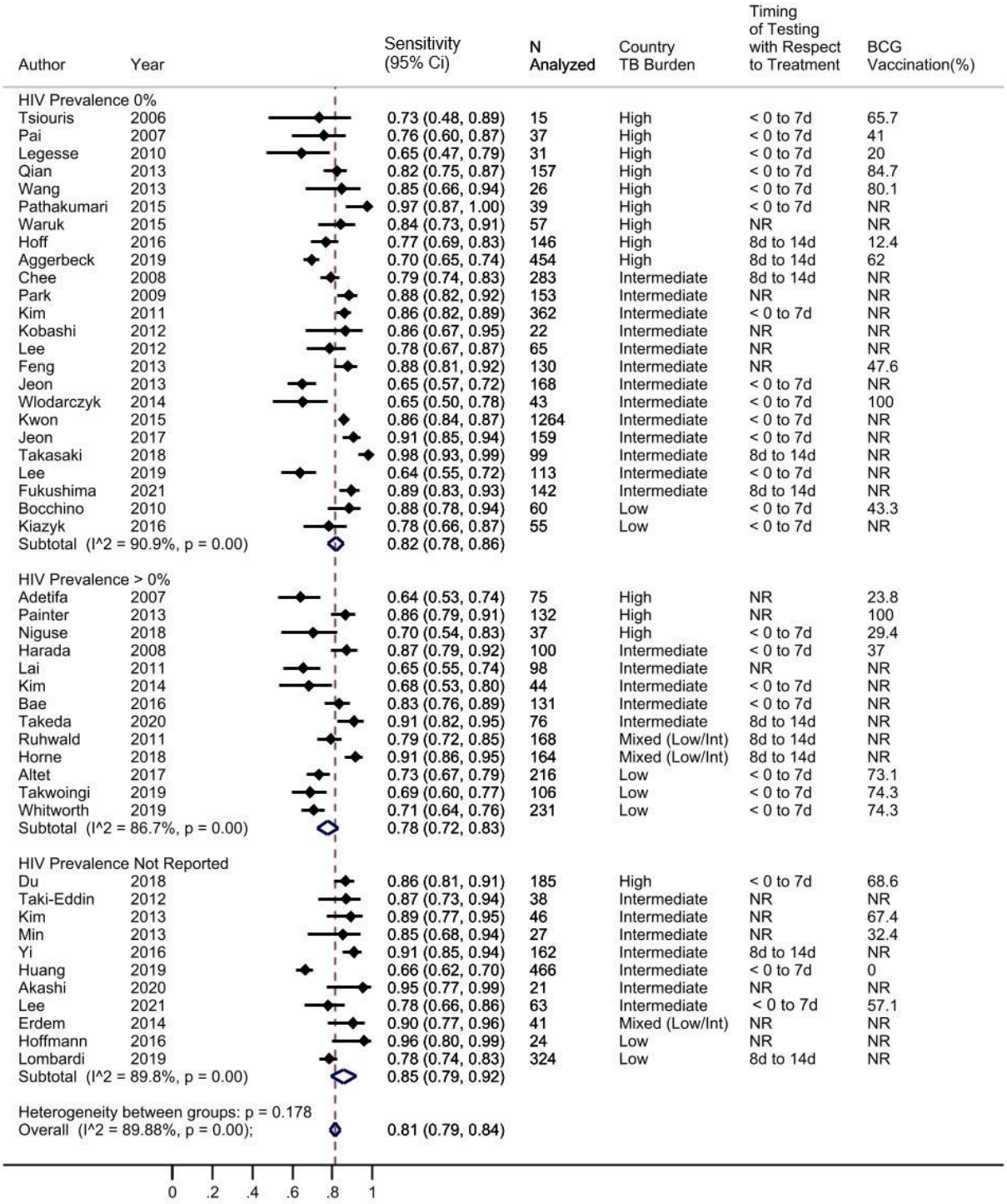
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 19. Sensitivity for QFT-Gold In-Tube (3rd Generation) Test, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



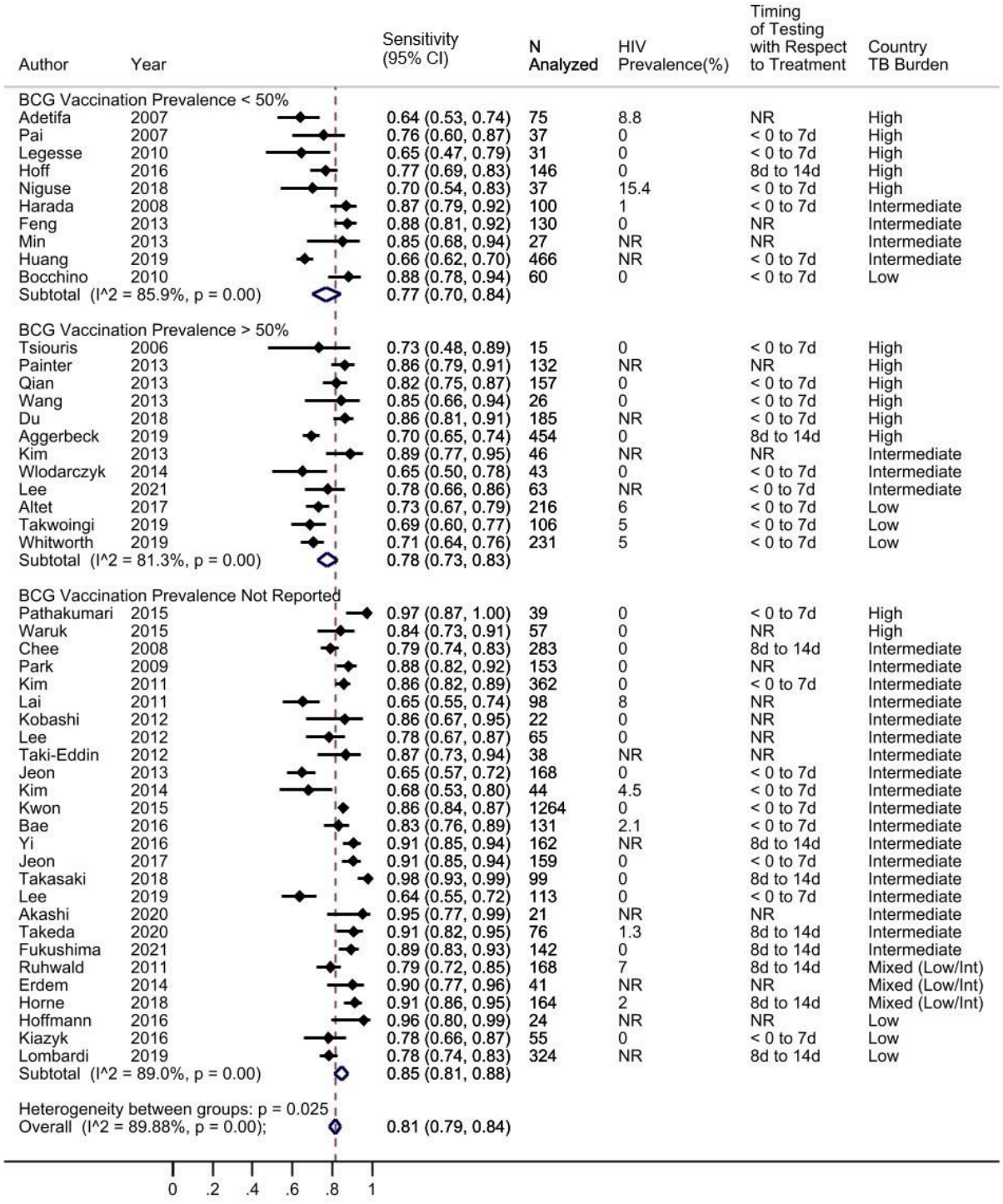
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; Int=intermediate; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 20. Sensitivity for QFT-Gold In-Tube (3rd Generation) Test, Stratified by HIV Prevalence of the Study Population



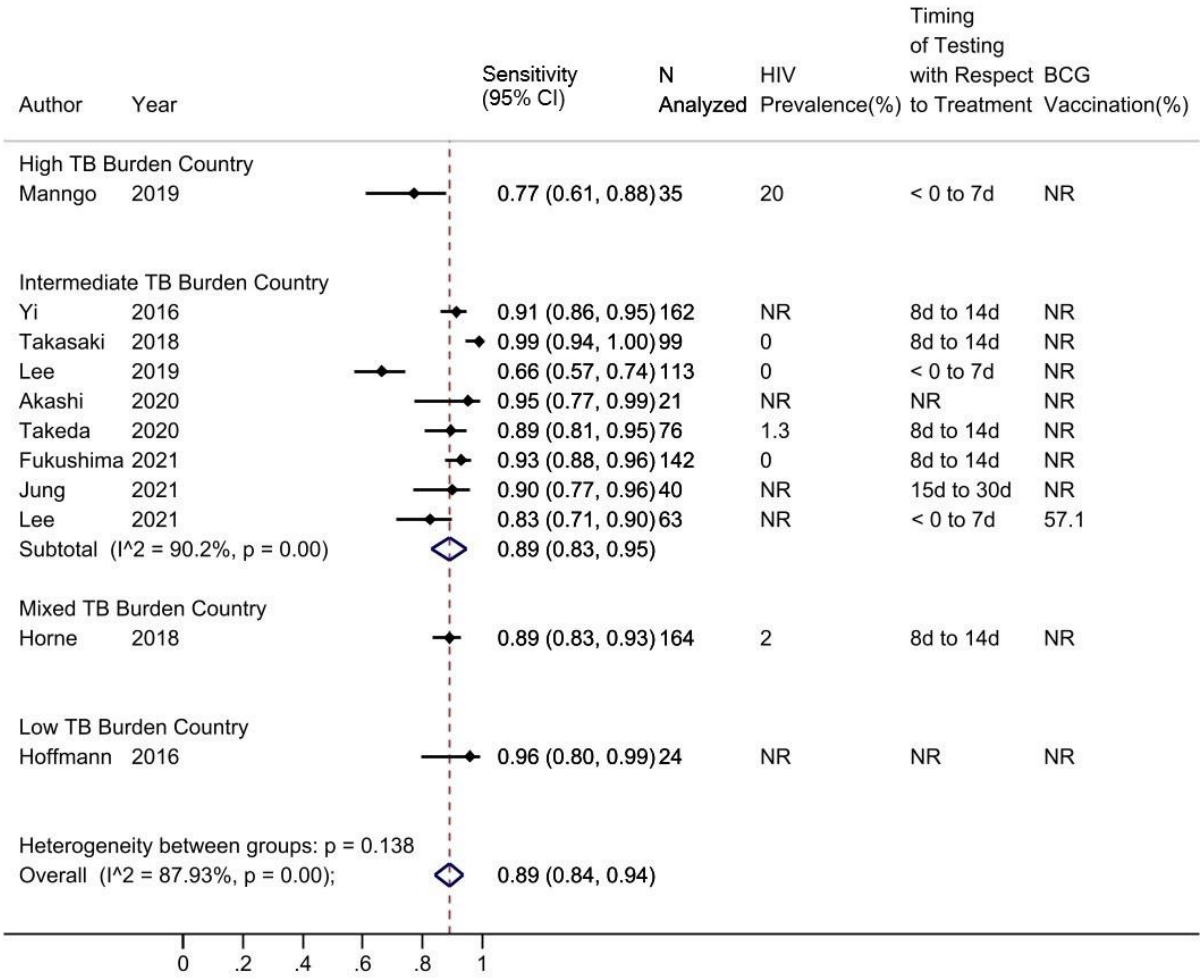
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; Int=intermediate; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 21. Sensitivity for QFT-Gold In-Tube (3rd Generation) Test, Stratified by BCG Vaccination Prevalence of the Study Setting



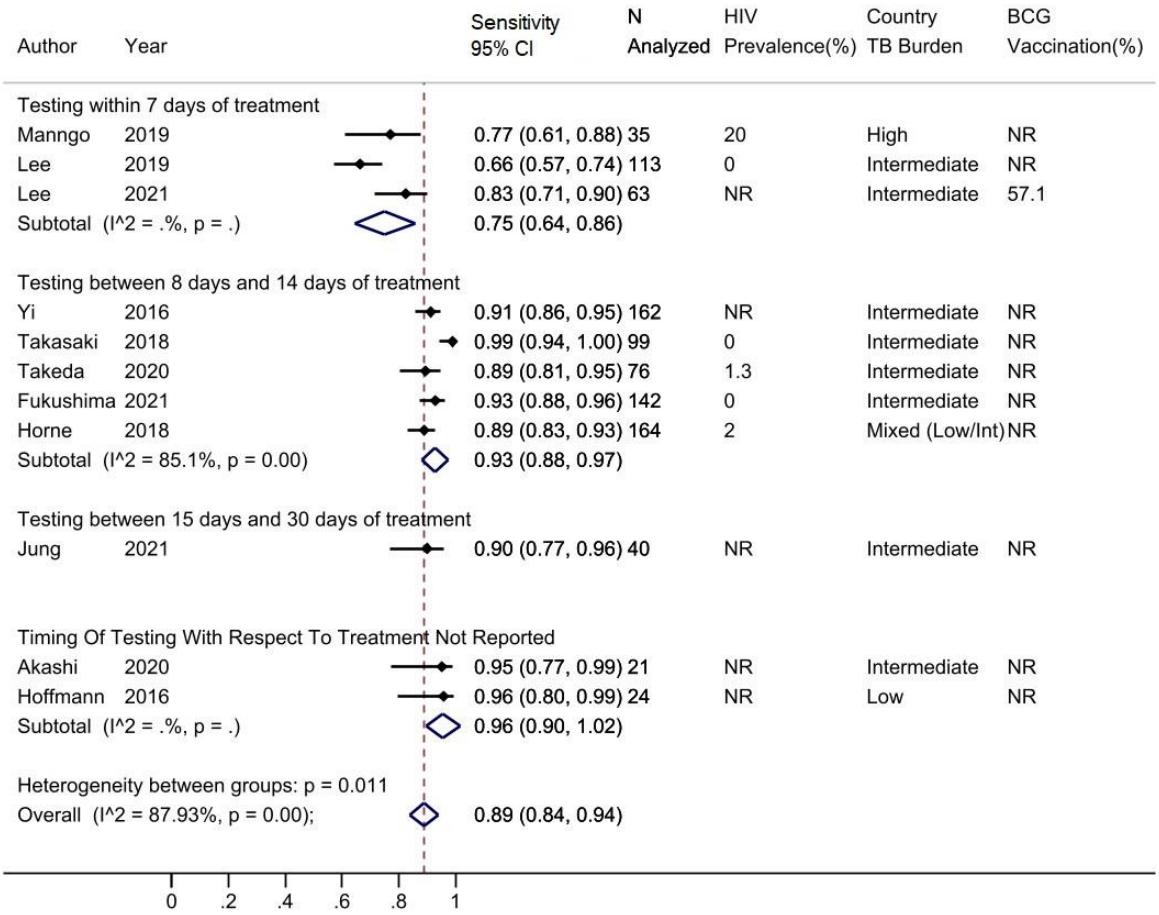
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; Int=intermediate; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 22. Sensitivity for QFT-Gold Plus (4th Generation) Test, Stratified by Country TB Burden of the Study Setting



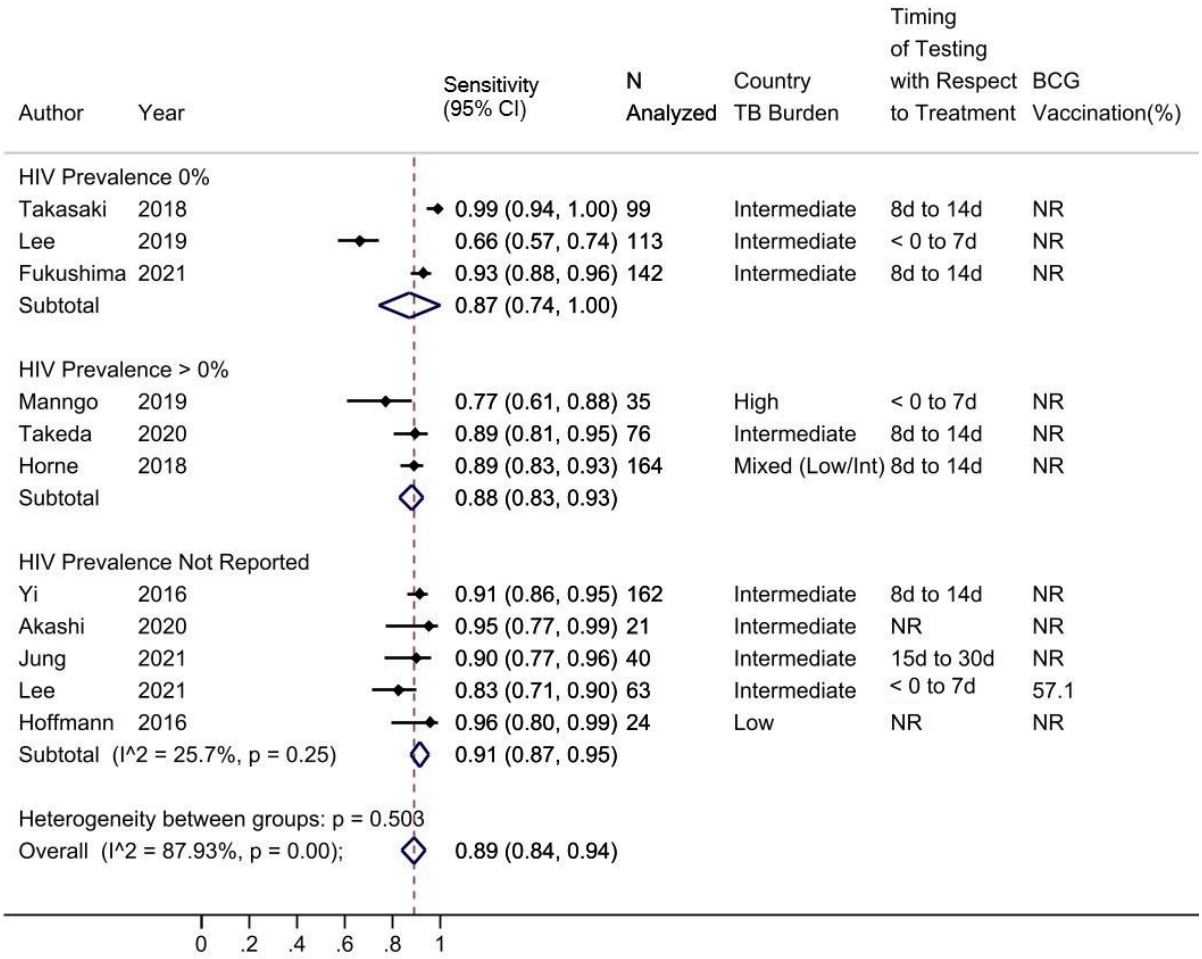
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 23. Sensitivity for QFT-Gold Plus (4th Generation) Test, Stratified by Timing of Testing With Respect to Antituberculosis Treatment



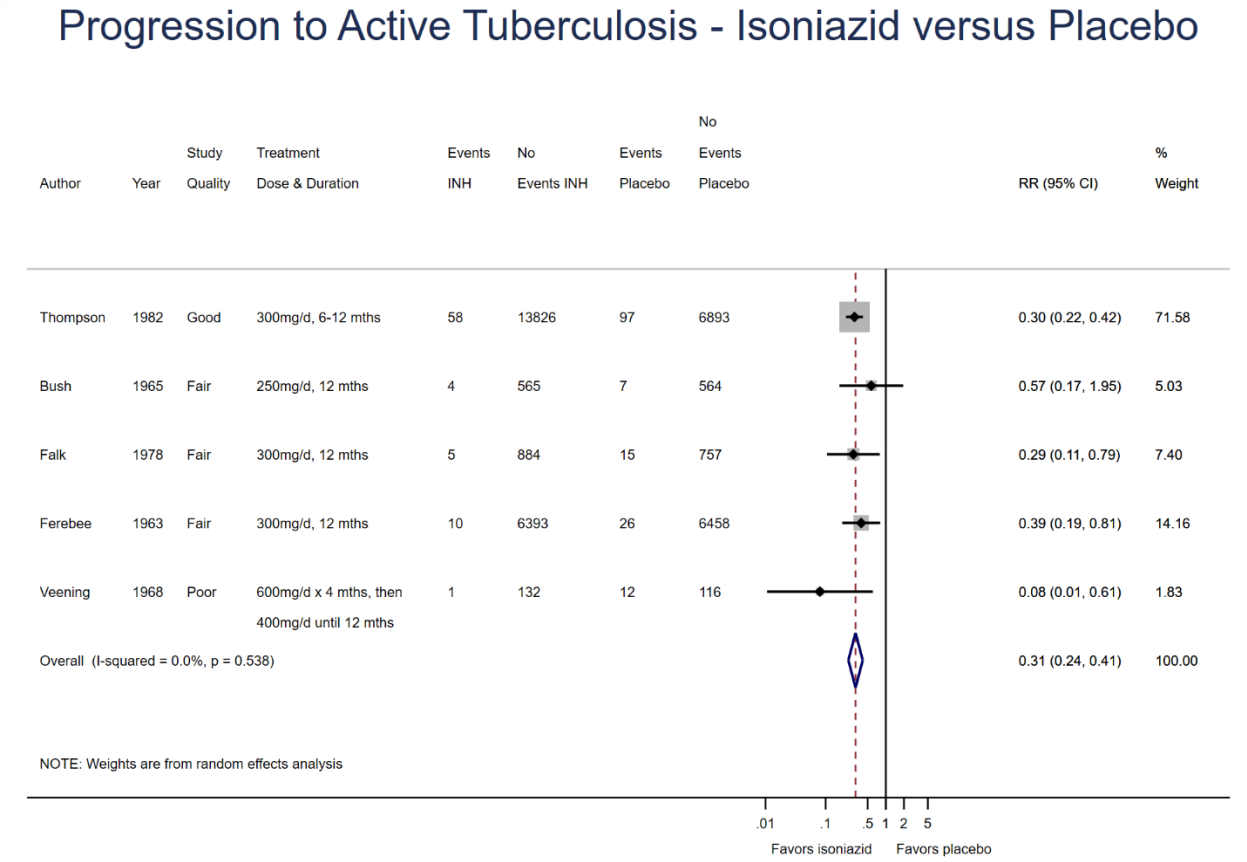
Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 24. Sensitivity for QFT-Gold Plus (4th Generation) Test, Stratified by HIV Prevalence of the Study Population



Abbreviations: BCG=Bacille Calmett-Guérin; CI=confidence interval; d=day; HIV=human immunodeficiency virus; I^2=the proportion of variation in study estimates due to heterogeneity; N=number; NR=not reported; QFT=QuantiFERON-TB; TB=tuberculosis; TST=tuberculin skin test.

Appendix F Figure 25. Isoniazid Compared With Rifampin: Relative Risk of Treatment Discontinuation Due to Adverse Events, Data From Three Randomized, Controlled Trials

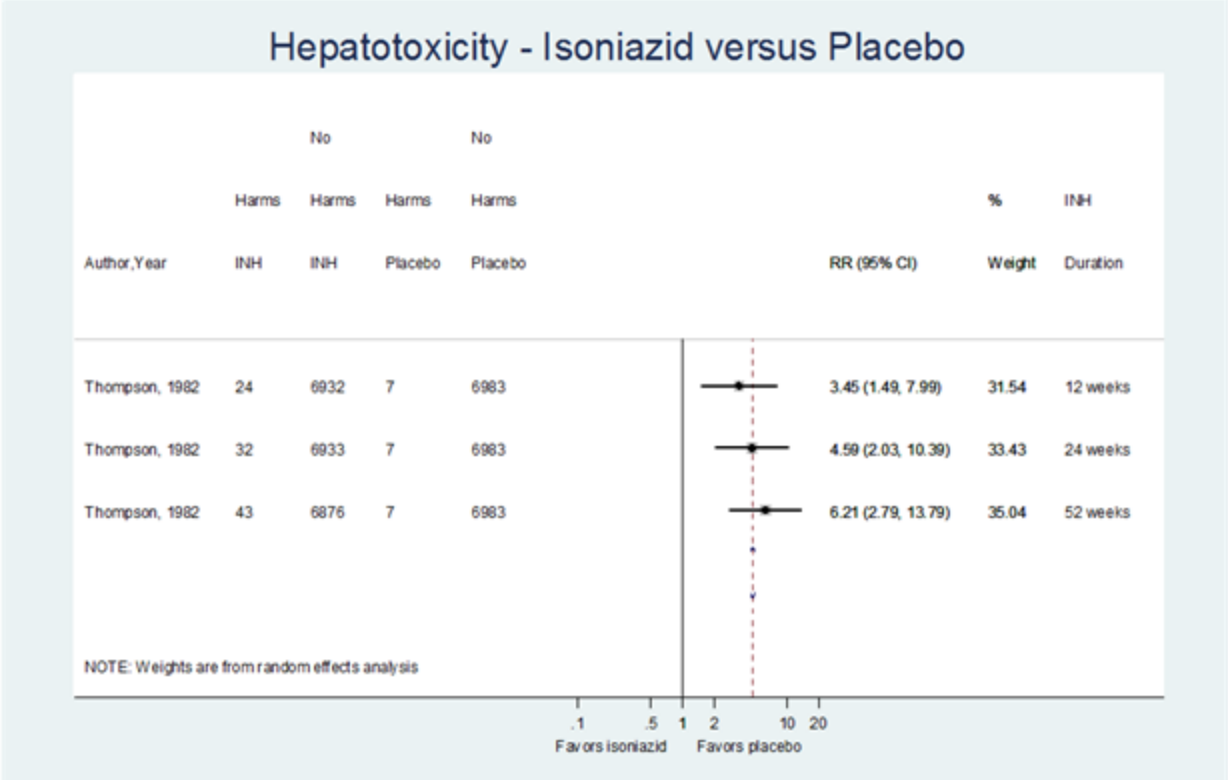


Notes: Marker size indicates relative sample size and contribution to pooled estimate. For Thompson (IUAT trial),[159] we included data from the 24- and 52-week groups. For Bush,[165] we only used data for those ≥20 years of age. For Falk,[166] we used data for the subset with no previous TB therapy for participants in the isoniazid 1-year group (we did not include data for the isoniazid 2-year group). For Ferebee,[31] 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 of the study were among adults).

For RCTs 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 those with confirmed LTBI, or that the vast majority of subjects (over 75 percent) were tuberculin positive. These trials met many of our eligibility criteria, but they all used a longer duration of treatment than is currently recommended by the CDC (i.e., they used 1 year or longer of isoniazid), and some used lower or higher doses than currently recommended or did not require LTBI confirmation for subjects to be eligible [31, 165, 166] One of the four trials was rated poor quality.[168]

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

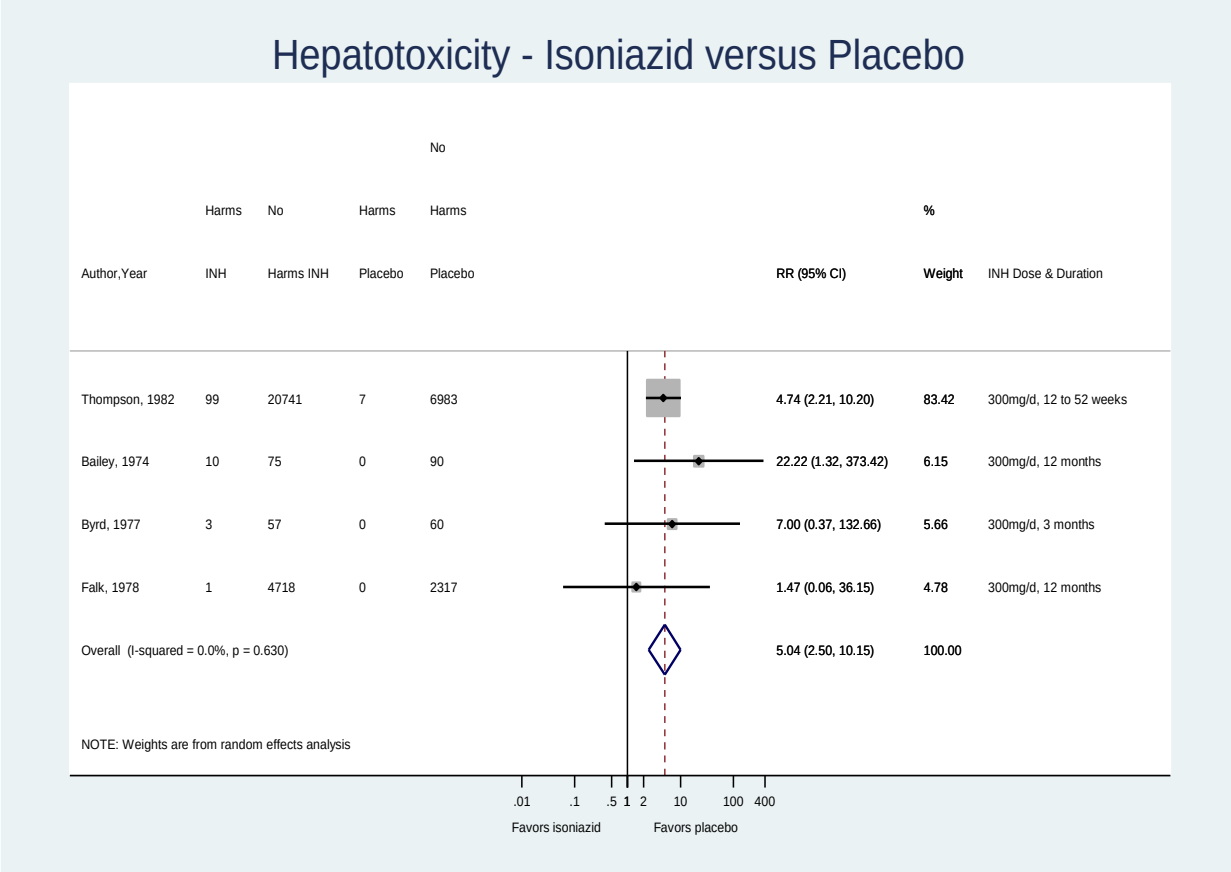
Appendix F Figure 26. Isoniazid Compared With Placebo: Relative Risk of Developing Hepatotoxicity in the IUAT Trial



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.

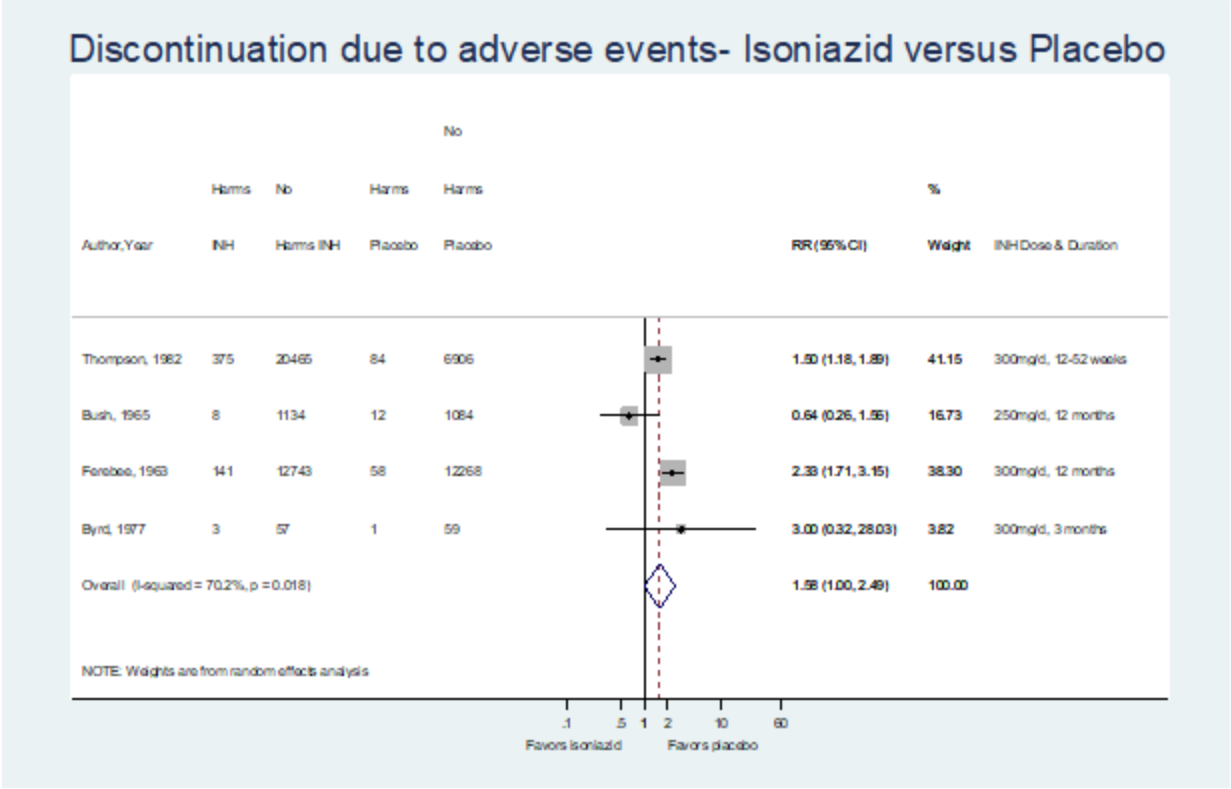
Appendix F Figure 27. Isoniazid Compared With Placebo, Relative Risk of Developing Hepatotoxicity: Sensitivity Analysis Including Data From Four Randomized, Controlled Trials



Notes: For Thompson, 1982 (IUAT trial),[159] 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,[185] and Byrd, 1977,[186] hepatotoxicity was defined as SGOT >100 mU/ml. For Falk, 1978,[166] hepatotoxicity was defined only as "mild hepatitis."

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

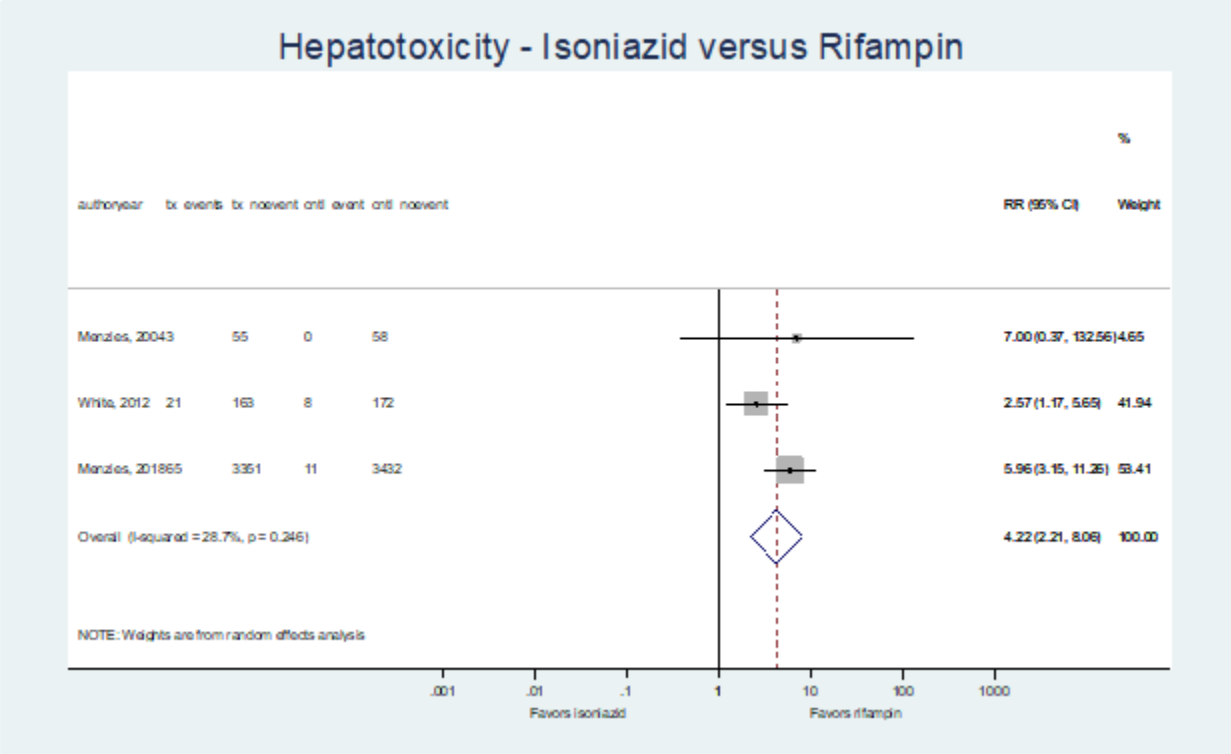
Appendix F Figure 28. Isoniazid Compared With Placebo, Relative Risk of Treatment Discontinuation Due to Adverse Events: Sensitivity Analysis Including Data From Four Randomized, Controlled Trials



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.

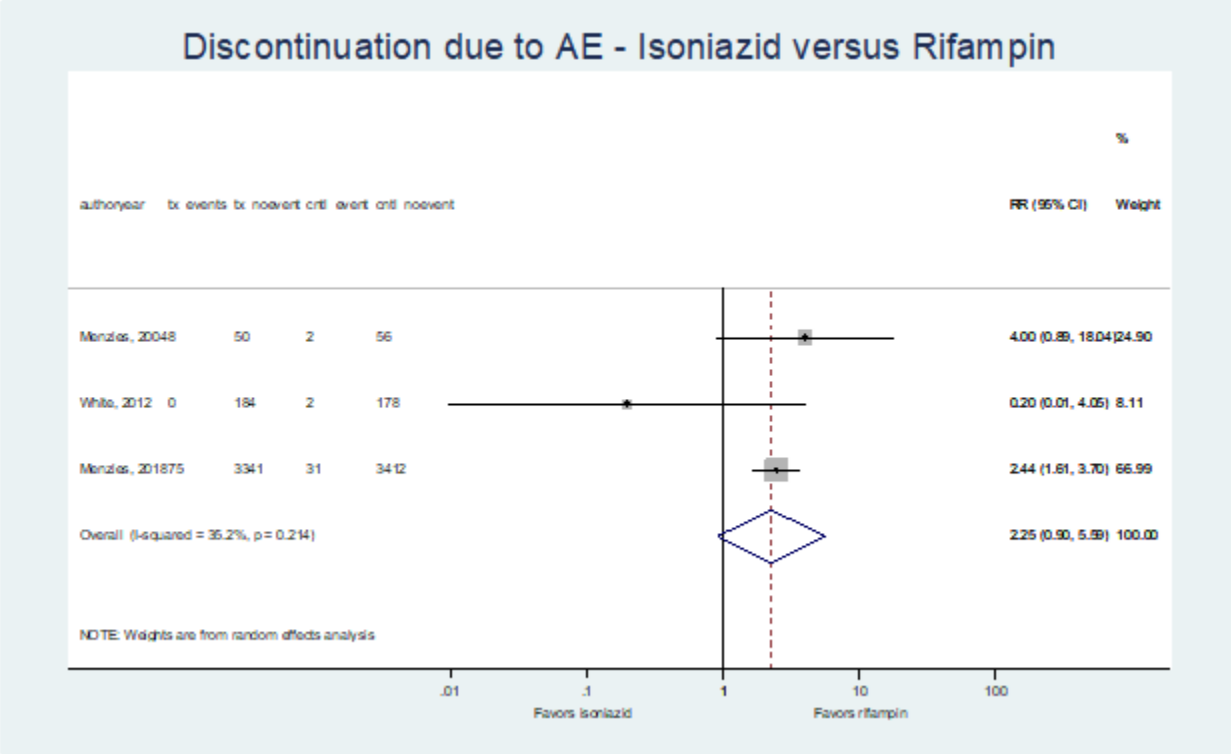
Abbreviations: CI=confidence interval; INH=isoniazid; IUAT=International Union Against Tuberculosis; RR=relative risk.

Appendix F Figure 29. Isoniazid Compared With Rifampin: Relative Risk of Developing Hepatotoxicity, Data From Three Randomized, Controlled Trials



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

Appendix F Figure 30. Isoniazid Compared With Rifampin: Relative Risk of Treatment Discontinuation Due to Adverse Events, Data From Three Randomized, Controlled Trials



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