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Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults

Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Five to ten percent of individuals with latent tuberculosis infection (LTBI) progress to active tuberculosis (TB) disease. Identifying and treating LTBI is a key component of the strategy for reducing the burden of TB disease.

OBJECTIVE To review the evidence about targeted screening and treatment for LTBI among adults in primary care settings to support the US Preventive Services Task Force in updating its 1996 recommendation.

DATA SOURCES MEDLINE, Cochrane Library, and trial registries, searched through August 3, 2015; references from pertinent articles; and experts. Literature surveillance was conducted through May 31, 2016.

STUDY SELECTION English-language studies of LTBI screening, LTBI treatment with recommended pharmacotherapy, or accuracy of the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs). Studies of individuals for whom LTBI screening and treatment is part of public health surveillance or disease management were excluded.

DATA EXTRACTION AND SYNTHESIS Two investigators independently reviewed abstracts and full-text articles. When at least 3 similar studies were available, random-effects meta-analysis was used to generate pooled estimates of outcomes.

MAIN OUTCOMES AND MEASURES Sensitivity, specificity, reliability, active TB disease, mortality, hepatotoxicity, and other harms.

RESULTS The review included 72 studies (n = 51 711). No studies evaluated benefits and harms of screening compared with no screening. Pooled estimates for sensitivity of the TST at both 5-mm and 10-mm induration thresholds were 0.79 (5-mm: 95% CI, 0.69-0.89 [8 studies, n = 803]; 10 mm: 95% CI, 0.71-0.87 [11 studies; n = 988]), and those for IGRAs ranged from 0.77 to 0.90 (57 studies; n = 4378). Pooled estimates for specificity of the TST at the 10-mm and 15-mm thresholds and for IGRAs ranged from 0.95 to 0.99 (34 studies; n = 23 853). A randomized clinical trial (RCT) of 24 weeks of isoniazid in individuals with pulmonary fibrotic lesions and LTBI (n = 27 830) found a reduction in absolute risk of active TB at 5 years from 1.4% to 0.5% (relative risk [RR], 0.35 [95% CI, 0.24-0.52]) and an increase in absolute risk for hepatoxicity from 0.1% to 0.5% (RR, 4.59 [95% CI, 2.03-10.39]) for 24 weeks of daily isoniazid compared with placebo. An RCT (n = 6886) found that 3 months of once-weekly rifapentine plus isoniazid was noninferior to 9 months of isoniazid alone for preventing active TB. The risk difference for hepatoxicity comparing isoniazid with rifampin ranged from 3% to 7%, with a pooled RR of 3.29 (95% CI, 1.72-6.28 [3 RCTs; n = 1327]).

CONCLUSIONS AND RELEVANCE No studies evaluated the benefits and harms of screening compared with no screening. Both the TST and IGRAs are moderately sensitive and highly specific within countries with low TB burden. Treatment reduced the risk of active TB among the populations included in this review. Isoniazid is associated with higher rates of hepatotoxicity than placebo or rifampin.

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Prevention of active tuberculosis (TB) by treating latent tuberculosis infection (LTBI) is a major goal of the strategy for eliminating TB.[1,2] Estimating the prevalence of LTBI is challenging because there is no direct test for latent infection, but US national survey data suggest a population prevalence of 4.7% (95% CI, 3.4%-6.3%) for the overall US population and 20.5% (95% CI, 16.1%-25.8%) for the foreign-born US population, based on a positive tuberculin skin test (TST) result.[3] Five percent to 10% of immunocompetent individuals with a positive TST result will develop active TB disease in their lifetime.[4] In developed countries with a low prevalence of TB, LTBI screening is recommended by the World Health Organization, American Thoracic Society, Infectious Diseases Society of America, and the Centers for Disease Control and Prevention (CDC) only for high-risk groups and when treatment is feasible.[5,6] Current screening tests for LTBI include the TST and interferon-gamma release assays (IGRAs). Individuals who screen positive are generally offered preventive treatment (eTable 1 in the Supplement) after active infection has been excluded.[7]

In 1996, the US Preventive Services Task Force (USPSTF) recommended screening with the TST for asymptomatic, high-risk individuals (A recommendation). To inform an updated recommendation, we reviewed the evidence on test accuracy and benefits and harms of screening and treatment for LTBI in settings and populations relevant to US primary care.

Methods

Scope of the Review

Detailed methods are available in the full evidence report at http://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review157/latent-tuberculosis-infection-screening. The analytic framework and key questions that guided the review are shown in **Figure 1**.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published from database inception through August 3, 2015. The search strategies for these databases are listed in the eMethods in the Supplement. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were also searched for unpublished literature. To supplement electronic searches, the reference lists of pertinent articles and all studies suggested by reviewers or comments received during public commenting periods were reviewed. Since August 2015, ongoing surveillance has been conducted through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on May 31, 2016, and no new studies were identified.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria for each key question (KQ) (eTable 2 in the Supplement). Disagreements about inclusion were resolved by discussion. Only studies rated as of fair or good quality were included. For the overarching question regarding direct evidence of benefits of screening (KQ1), only randomized clinical trials (RCTs) or prospective cohort studies that compared screening with no screening in primary care settings and focused on asymptomatic adults belonging to populations at increased risk for developing active TB were eligible. Primary care was broadly defined to include public health settings or specialized clinics providing primary care functions (eg, prison clinics). Studies in which more than 25% of the study population were younger than 18 years or were known to be human immunodeficiency virus (HIV) positive were excluded, unless results were stratified by these characteristics. Studies on close contacts of individuals with active TB were excluded because testing and treatment of such populations is considered a public health surveillance activity. Studies of individuals with underlying immunosuppression and for whom LTBI screening and treatment would be part of disease management were also excluded, for example, studies of individuals beginning treatment with tumor necrosis factor–alpha inhibitors. Other populations at increased risk were included, such as persons who had previously received the bacillus Calmette–Guérin (BCG) vaccination, injection drug users, persons who were homeless or residing in homeless shelters, former prisoners, persons born in or former residents of countries with high TB prevalence, persons who worked with such individuals, and persons with a documented increased risk for progression from LTBI to active TB.

For screening test accuracy and reliability (KQ2), studies assessing the TST using the Mantoux method and 3 IGRAs were included.[8] Because there is no direct reference test for latent infection, we relied on studies of individuals with bacteriologically confirmed active TB conducted in any country or setting for sensitivity and on studies of healthy participants at low risk for TB and TB exposure that were conducted in countries not considered as having high TB burden for specificity.[8,9] Reliability was defined as the degree to which a test provided stable and consistent results, including outcomes such as test-retest reliability, interrater reliability, and interlaboratory reliability.

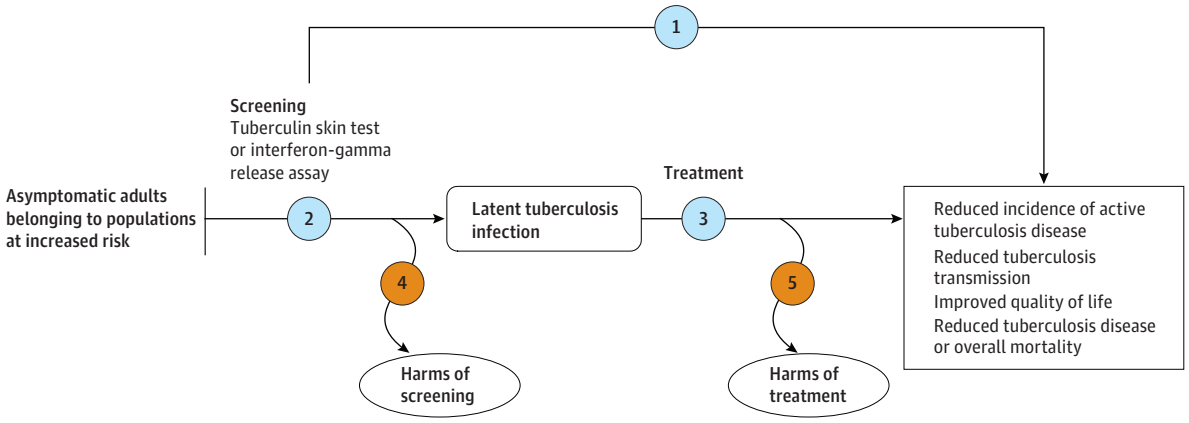
To review the benefits (KQ3) and harms (KQ5) of treatment, RCTs of individuals with LTBI that compared a CDC-recommended treatment (medication, dose, and duration) with placebo, delayed treatment, no treatment, or another CDC-recommended treatment were included. For harms of treatment (KQ5), prospective cohort studies and case-control studies were also eligible. For harms associated with screening (KQ4), systematic reviews, RCTs, and prospective cohort studies reporting false-positive results leading to unnecessary testing (eg, chest radiography) or treatment, labeling, stigma, anxiety, or cellulitis were eligible.

Except for studies of screening test accuracy and reliability (KQ2), studies conducted in countries categorized as anything other than "very high" on the United Nations Human Development Index[10] were excluded.

Data Extraction and Quality Assessment

For each included study, one investigator extracted information about design, population, tests or treatments used, and outcomes (eg, sensitivity, specificity, active TB), and a second investigator reviewed for completeness and accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this

Figure 1. Analytic Framework and Key Questions



Key questions

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

2 a. What is the accuracy and reliability of the TST or the interferon-gamma release assay (IGRA) for screening asymptomatic adults who are at increased risk for developing active TB disease?

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

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

4 Are there harms associated with screening for LTBI?

a. Do these harms differ by screening method or strategy?

b. Do these harms differ by population?

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

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. CDC indicates Centers for Disease Control and Prevention. Further details are available from the USPSTF procedure manual.[106]

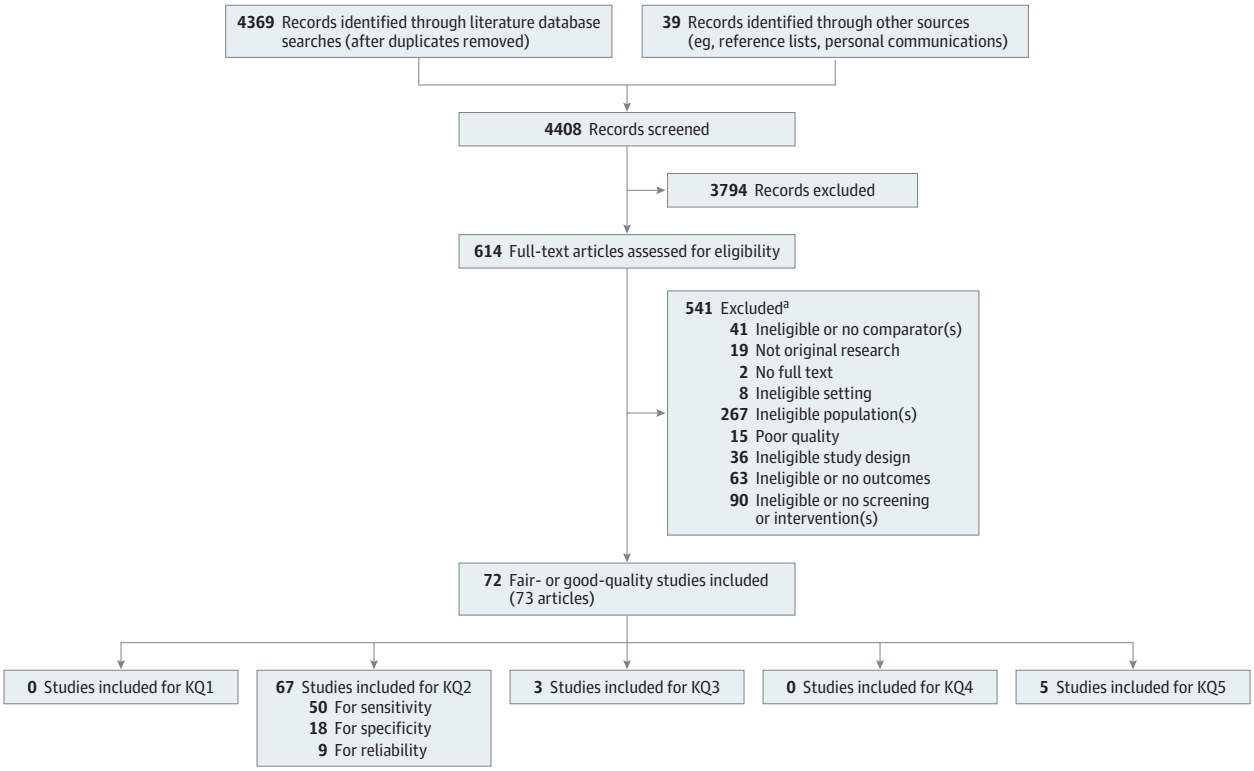
topic (eTable 3 in the Supplement).[11] Individual study quality ratings are provided in eTables 4-7 in the Supplement.

Data Synthesis and Analysis

Findings for each question are summarized in tabular and narrative form. To determine whether meta-analyses were appropriate, the number of studies available and the clinical and methodological heterogeneity of the studies following established guidance were assessed.[12] To do this, the populations, similarities and differences in screening tests or treatments used, and similarities in outcomes and timing of measured outcomes, were qualitatively assessed. When at least 3 similar studies were available, quantitative synthesis was conducted with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to determine pooled estimates.[12,13] Statistical heterogeneity was assessed using the I^2 statistic. Results for benefits and harms of treatment (KQ3 and KQ5) were considered statistically significant if the *P* value was less than .05 based on 2-sided testing. All quantitative analyses were conducted using Stata version 13.1 (StataCorp).[14]

Sensitivity analyses for screening test accuracy (KQ2) added in 19 studies rated as poor quality to determine whether inclusion of such studies would have altered conclusions. For benefits (KQ3) and harms (KQ5) of treatment, sensitivity analyses also added 6 RCTs comparing isoniazid with placebo that were either poor quality, did not meet all of the inclusion criteria, or both, because they used a longer duration of treatment than is currently recommended (eg, they used 1 year of isoniazid[15-19] or 3 months of isoniazid[20]); some also used lower or higher doses than currently recommended.[16,17] For RCTs to be included in sensitivity analyses, they either confirmed LTBI for participants to be eligible (eg, by enrolling only those who were TST positive), reported data for those with confirmed LTBI (eg, for the TST-positive subset of participants), or the vast majority of participants (more than 75%) were TST positive.

Figure 2. Literature Flow Diagram



[a] Nineteen studies that were poor quality, ineligible, or both were excluded but used in sensitivity analyses.

For all quantitative syntheses, sensitivity analyses were conducted using maximum likelihood random-effects (KQ2) or profile likelihood random-effects methods (KQs 3 and 5) because DerSimonian and Laird models may not perform well when few studies are included.[21-25] Results were essentially the same as for those using DerSimonian and Laird random-effects models, with some minor variation in width of confidence intervals for some estimates, and thus are not reported further.

Results

Study selection included reviewing 4408 titles and abstracts and 614 full-text articles (**Figure 2**). Of the 72 fair- or good-quality studies that met inclusion criteria (n = 51 711), 67 were observational studies of screening test characteristics (KQ2). Five studies were RCTs focused on the benefits (KQ3) or harms (KQ5) of pharmacotherapy for LTBI. No eligible studies for KQ1 (direct evidence of screening for LTBI) or KQ4 (harms of screening) were identified.

Benefits of Screening

Key Question 1. Is there direct evidence that targeted screening for LTBI in primary care settings in asymptomatic adults at increased risk for developing active TB improves quality of life or reduces active TB disease, transmission of TB, or disease specific or overall mortality?

No eligible studies were identified.

Accuracy and Reliability of Screening Tests

Key Question 2. What is the accuracy and reliability of the TST or IGRA (KQ2a) or sequential screening strategies (KQ2b) for screening asymptomatic adults who are at increased risk for developing active TB disease?

No eligible studies evaluating sequential screening strategies were identified. Fifty studies (n = 4167) related to the sensitivity of the TST or IGRA tests were identified; detailed individual study characteristics are provided in eTables 8 and 9 in the Supplement. Eight studies were conducted in high TB-burden countries,[26-33] 29 were conducted in countries with intermediate TB burden,[34-62] and 10 were conducted in countries with low TB burden,[63-72] including 4 in the United States. Three multinational studies were conducted in countries with a mix of low and intermediate TB burden.[73-75] In 3 studies, fewer than 25% of the participants were BCG vaccinated.[28,30,72] Thirteen studies included study populations that were between 25% and 75% vaccinated,[27,29,34,36,38,39,43,56,58,59,65,70,71] and 12 studies included study populations that had more than 75% of participants vaccinated.[26,32,33,40-42,45,51,52,61,66,74] Twenty-two studies did not report the BCG vaccination prevalence in the study population.

Pooled estimates were calculated for sensitivity of the TST by induration threshold and of IGRAs by assay (**Table 1**). The pooled sensitivity for the TST with a 5-mm threshold was 0.79 (95% CI, 0.69-0.89; I^2 = 94.6% [8 studies; n = 803]); for the 10-mm threshold, 0.79 (95% CI, 0.71-0.87; I^2 = 91.4% [11 studies; n = 988]); and for 15-mm threshold, 0.52 (95% CI, 0.35-0.68, I^2 = 95.5% [7 studies; n = 740]) (eFigure 1 in the Supplement). For the T-SPOT.*TB* IGRA, there was

Table 1. Summary of Pooled Test Characteristics (Key Question 2) for Various Thresholds of Tuberculin Skin Test and Interferon-Gamma Release Assays Among Patients With Bacteriologically Confirmed Tuberculosis (Sensitivity) and Healthy Participants Without Tuberculosis Risks or Exposures (Specificity)

Test	Sensitivity				Specificity			
	No. of Studies	Participants, No.	Pooled Estimate (95% CI)	I^2, %	No. of Studies	Participants, No.	Pooled Estimate (95% CI)[a]	I^2, %
TST induration threshold, mm								
5	8	803	0.79 (0.69-0.89)	94.6	4	47[40]	0.30 (0.19-0.44)	NA
						2848[65]	0.95 (0.94-0.96)	
						1750[76]	0.94 (0.92-0.95)	
						551[77]	0.97 (0.95-0.98)	
10	11	988	0.79 (0.71-0.87)	91.4	9[b]	9651	0.97 (0.96-0.99)	94.3
15	7	740	0.52 (0.35-0.68)	95.5	12	9640	0.99 (0.98-0.99)	91.7
IGRA								
T-SPOT.*TB*	16[c]	984	0.90 (0.87-0.93)	63.6	5	1810	0.95 (0.92-0.98)	79.1
QuantiFERON TB Gold	17	1073	0.77 (0.74-0.81)	55.3	4	699	0.98 (0.90-1.0)[d]	NA[d]
QuantiFERON TB Gold In-Tube	24	2321	0.80 (0.77-0.84)	74.3	4	2053	0.97 (0.94-0.99)	93.4

Abbreviations: I^2, proportion of variation in study estimates due to heterogeneity; IGRA, interferon-gamma release assay; NA, not applicable; TST, tuberculin skin test.

[a] Individual study estimates are reported for 5-mm TST induration threshold (studies were not pooled for this outcome because 1 study estimate from a country with intermediate tuberculosis burden was much lower than the estimates from countries with low tuberculosis burden).

[b] One study[78] could not be included in the DerSimonian-Laird pooled estimate owing to a point estimate of 1.0 for specificity (95% CI, 0.99-1.00). The estimate using the maximum likelihood approach, which can accommodate point estimates of 1.0, was similar (pooled specificity, 0.97 [95% CI, 0.93-0.99]).

[c] One study[69] could not be included in the pooled estimate owing to a point estimate of 1.0 for sensitivity (95% CI, 0.69-1.0). The estimate using the maximum likelihood approach, which can accommodate point estimates of 1.0, was similar (pooled sensitivity, 0.90 [95% CI, 0.86-0.93]).

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

no difference in estimates based on whether the US Food and Drug Administration or European threshold for a positive test was used, so all studies were combined for a pooled estimate of 0.90 (95% CI, 0.87-0.93; I^2 = 63.6% [16 studies; n = 984]) (eFigure 2 in the Supplement). The pooled estimate for sensitivity of the QuantiFERON TB Gold IGRA was 0.77 (95% CI, 0.74-0.81; I^2 = 55.3% [17 studies; n = 1073]) and of the QuantiFERON TB Gold In-Tube IGRA was 0.80 (95% CI, 0.77-0.84; I^2 = 74.3% [24 studies; n = 2321]) (eFigure 2 in the Supplement). The percentage of IGRA tests with indeterminate results ranged from 3% to 7% in studies reporting this information.

Because there was moderate to substantial statistical heterogeneity, results for all tests were stratified based on factors consistently reported across studies that could affect the accuracy of the test, including whether testing occurred after anti-TB treatment had been started, the TB burden of the country where study took place, and BCG vaccination prevalence among the study population. Detailed findings related to these analyses are in the full evidence report. For some tests, estimates for sensitivity were higher in countries with low TB burden compared with countries with intermediate or high TB burden. For example, sensitivity for the TST at the 10-mm induration threshold was 0.88 (95% CI, 0.76-0.99 [3 studies; n = 424]) in low-burden countries, compared with 0.72 in intermediate-burden countries (95% CI, 0.65-0.79 [6 studies; n = 416]).

Eighteen studies related to the specificity of the TST or IGRA tests were identified (n = 10 693); detailed individual study characteristics are provided in eTables 10 and 11 in the Supplement. Fourteen of the 18 studies evaluating specificity were conducted in countries with low TB burden (10 were in the United States).[64,65,76-87] BCG vaccination rates were more than 75% in 4 studies,[40,45,58,76] less than 5% in 9 studies,[64,65,77,78,80,82-85] and not reported in 5 studies.[73,79,86-88] Pooled estimates were calculated for specificity of the TST by test threshold and of IGRAs by assay (Table 1).

The pooled specificity for the TST with a 10-mm threshold was 0.97 (95% CI, 0.96-0.99; I^2 = 94.3% [9 studies; n = 9651]); for the 15-mm threshold, 0.99 (95% CI, 0.98-0.99; I^2 = 91.7% [12 studies; n = 9640]); individual study estimates are provided in eFigure 3 in the Supplement. The pooled estimate for specificity was 0.95 (95% CI, 0.92-0.98; I^2 = 79.1% [5 studies; n = 1810]) for the T-SPOT *TB* IGRA; 0.98 (95% CI, 0.90-1.0 [4 studies; n = 699]) for the QuantiFERON TB Gold IGRA; and 0.97 (95% CI, 0.94-0.99; I^2 = 93.4% [4 studies; n = 2053]) for the QuantiFERON TB Gold In-Tube IGRA; individual study estimates are provided in eFigure 3 in the Supplement. The percentage of IGRA tests with indeterminate results ranged from 0% to 3% in studies reporting this information. Because of substantial heterogeneity, results were stratified based on country TB burden and BCG vaccination rates. Across all tests, specificity was substantially lower in countries with intermediate TB burden than in those with low TB burden. Although the populations of studies conducted in intermediate-burden countries also had high prevalence of BCG vaccination, the available evidence did not allow definitive conclusions about the influence of BCG vaccination on specificity estimates because BCG vaccination status was not consistently reported across studies.

Nine studies (n = 4079) were identified that assessed the reliability for at least 1 of the included screening tests.[45,80,84,85,89-93] Individual study characteristics are provided in eTable 12 in the Supplement. Overall reliability varied by test and by type of reliabil-

ity outcome. Three studies (n = 1826,[80] n = 1189,[85] and n = 127[84]) measured the interrater reliability for TST results by reporting the κ statistic for agreement by TST reaction size; results ranged from 0.55 to 0.79, indicating moderate to substantial agreement between 2 observers. One study (n = 91) evaluated the interlaboratory reliability of the QuantiFERON TB Gold In-Tube IGRA by sending 3 blood specimens from each participant to 3 different laboratories noted to have extensive experience and proficiency with IGRA testing and interpretation.[91] Across all 3 laboratories, 7.7% of participants had discordant results (none had indeterminate results); κ values of pairwise laboratory sample comparisons ranged from 0.87 to 0.93.[91] One study (n = 130) assessed the reliability of IGRA results by processing 2 blood samples from each study participant (using the same laboratory and same type of test interpretation); 5.8% of participants had discordant results for the QuantiFERON TB Gold In-Tube IGRA, and 6.5% had discordant results for T-SPOT.*TB*.[89] Additional reliability results are provided in the eResults in the Supplement.

Benefits of Treatment

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

Study characteristics of trials evaluating the benefits of treatment are reported in **Table 2**. Three RCTs that evaluated the benefits of treatment for LTBI were included; 1 compared isoniazid with placebo (n = 27 830)[97]; 1 compared rifampin with isoniazid (n = 847)[95]; and 1 compared rifapentine plus isoniazid with isoniazid alone (n = 6886).[96] No studies reported benefits related to quality of life or TB transmission.

The International Union Against Tuberculosis (IUAT) trial randomized 27 830 adults with fibrotic pulmonary lesions and a 6-mm or greater Mantoux TST induration, but without active TB or previous anti-TB treatment, to 4 groups: placebo or isoniazid (300 mg daily) for 12 weeks, 24 weeks (currently a CDC-approved regimen), or 52 weeks.[97] The median age was 50 years, and 53% were men. After 5 years, 1.4% of the placebo group and 0.5% of the 24-week treatment group developed active TB, for a relative risk of 0.35 (95% CI, 0.24-0.52; number needed to treat, 112). Individuals with larger fibrotic lesions had a greater risk of developing active TB; the incidence of active TB in the placebo group was approximately half as great among individuals with lesions less than 2 cm^2 (11.6 per 1000) as among individuals with larger lesions (21.3 per 1000). There were no deaths attributable to TB in any of the isoniazid groups; 3 individuals died of TB in the placebo group. One open-label trial randomized 847 participants to 4 months of rifampin or 9 months of isoniazid to compare adverse events and treatment completion.[95] It reported zero deaths from TB in either group, zero deaths (due to any cause) in the rifampin group, and 1 death in the isoniazid group.

The PREVENT TB study was an open-label, noninferiority RCT that randomized 7731 individuals to directly observed once-weekly rifapentine plus isoniazid for 3 months or to daily self-administered isoniazid for 9 months.[96] Most participants (89%) were from the United States or Canada and were high-risk individuals with a positive TST result. Most (71%) had a close contact with a patient with active TB within 2 years; 25% were included solely because of conversion to skin-test positivity. Risk factors for TB included a history of incarceration (5.1%), injection-drug use (3.7%), and homelessness (27.8%). Data were obtained from the CDC for the subset of participants most directly relevant for this review: the 6886 adults (18 years or older) who were HIV negative and TST or IGRA positive. The median age for this subset was 37 years; 54.2% were men, and 57% were white. For this subset, active TB developed in 5 individuals in the combination-therapy group and 10 individuals in the isoniazid-only group over 33 months of follow-up. The combination therapy was found to be noninferior to isoniazid-only treatment. Overall mortality was similar for the 2 groups (30 participants vs 34 participants, respectively; $P = .42$).

Four RCTs identified as comparing isoniazid with placebo did not meet all eligibility criteria (mainly because of duration of treatment or dose as described in the Methods) but were used in sensitivity analyses (eTable 13 in the Supplement).[15-18] Sensitivity analyses using data from the 24- and 52-week groups from the IUAT trial and from these 4 additional RCTs found a relative risk (RR) of 0.31 (95% CI, 0.24-0.41; 36 823 participants) and no statistical heterogeneity in effects between studies ($I^2 = 0.0\%$) (eTable 14 and eFigure 4 in the Supplement).

Harms of Screening

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

No eligible studies were identified.

Harms of Treatment

Key Question 5. Are there harms associated with treatment for LTBI with CDC-recommended pharmacotherapy?

Study characteristics of trials evaluating the harms of treatment are reported in Table 2. Five RCTs were included.[94-98] One compared isoniazid with placebo (n = 27 830)[97]; 3 compared rifampin with isoniazid (n = 1327)[94,95,98]; and 1 compared rifapentine plus isoniazid with isoniazid alone (n = 6886).[96]

The IUAT trial (described above) reported the RRs for developing hepatitis (undefined by study authors) associated with isoniazid compared with placebo as 3.45 (95% CI, 1.49-7.99) for 12 weeks of treatment, 4.59 (95% CI, 2.03-10.39) for 24 weeks (number needed to harm [NNH], 279), and 6.21 (95% CI, 2.79-13.79) for 52 weeks. Mortality rates from hepatitis were 0.03% for the 12-week isoniazid treatment group, 0.0% for the 24-week treatment group, and 0.01% for the 52-week treatment group (zero deaths from hepatitis among placebo-treated patients). The mortality rate from hepatitis was 0.14 per 1000 persons receiving isoniazid (RR, 2.35 [95% CI, 0.12-45.46]; NNH, 6947). Sensitivity analyses for isoniazid compared with placebo for hepatitis using data from the IUAT trial (3 treatment groups combined) and 3 additional RCTs[15,19,20] that did not meet all eligibility criteria (eTables 13 and 15 in the Supplement) found an RR of 5.04 (95% CI, 2.50-10.15 [4 studies, 35 161 participants]) and no statistical heterogeneity among studies ($I^2 = 0.0\%$; $P = .63$).

In the IUAT trial, discontinuation because of adverse events was reported for 345 patients (1.8%) receiving isoniazid compared with 84 patients (1.2%) receiving placebo (RR, 1.50 [95% CI, 1.18-1.89]; NNH, 167). The most common reason was gastrointestinal distress (1.2% receiving isoniazid vs 0.9% placebo; RR, 1.33 [95% CI, 1.01-1.75]).

Table 2. Study Characteristics of Randomized Clinical Trials of Benefits (Key Question 3) and Harms (Key Question 5) of Treatment

Source	Population	TB Risk Factors, No. (%)	Age, y	Men, No. (%)	Follow-up	LTBI Confirmed	Country (TB Burden)[a]	Quality[b]
Menzies et al,[94] 2004 (n = 116 participants)	≥18 y; race/ethnicity NR	Randomization stratified by TB risk (high if HIV-infected close contacts with active TB[c] or fibronodular changes on chest radiograph)			4-9 mo	Yes (positive TST ≥5, 10, or 15 mm, with physician recommendation for treatment based on Canadian guidelines)	Canada (low)	Fair
Rifampin (10 mg/kg), up to 600 mg/d ×4 mo	BCG vaccination: 12 (21%) yes, 11 (19%) unknown	Contact with active TB case: 10 (17) High TB burden country of birth:[a] 45 (78) Abnormal chest radiograph: 29 (50)	32.9 (SD, 10.8)	36 (62)				
Isoniazid (5 mg/kg), up to 300 mg/d ×9 mo	BCG vaccination: 16 (28%) yes, 12 (21%) unknown	Contact with active TB case: 10 (17) High TB burden country of birth:[a] 48 (83) Abnormal chest radiograph: 31 (53)	34.8 (SD, 13.0)	29 (50)				
Menzies et al,[95] 2008 (n = 847 participants)	≥18 y; race/ethnicity NR				4-9 mo	Yes (positive TST and physician recommendation for treatment based on national or international guidelines)	Canada (low)[d]; Saudi Arabia (interme-diate); Brazil (high)	Good
Rifampin (10 mg/kg), up to 600 mg/d ×4 mo	BCG vaccination: 224 (54%) yes, 95 (33%) unknown	HIV infection: 6 (1) Abnormal chest radiograph: 117 (28) Contact with active TB case: 131 (31) Recent immigrant: 29 (7) Canadian participants (who comprised 80% of the sample) born in high TB incidence country: 227 (54)	18-34 y: 229 (55%) ≥35 y: 191 (45%)	218 (52)				
Isoniazid (5 mg/kg), up to 300 mg/d ×9 mo	BCG vaccination: 199 (47%) yes, 107 (25%) unknown	HIV infection: 7 (2) Abnormal chest radiograph: 105 (25) Contact with active TB case: 135 (32) Recent immigrant: 33 (8) Canadian participants (who comprised 80% of the sample) born in high TB incidence country: 235 (55)	18-34 y: 242 (57%) ≥35 y: 185 (43%)	228 (53)				
Sterling et al,[96] 2011 (PREVENT TB)[e] (n = 6886 participants)	≥18 y; close contacts of patients with culture-confirmed TB, recent converters, and small percentage with fibrosis; 2957 (42.9%) nonwhite BCG vaccination NR				33 mo	Yes (TST or IGRA positive)	United States (low); Canada (low); Brazil and Spain (low to high)	Fair
Rifapentine (900 mg/wk) + isoniazid (900 mg/wk) ×12 wk		Contact with active TB case: 2549 (71.7) Recent TST conversion: 918 (25.8) Fibrosis: 89 (2.5)	Median, 37	1951 (54.9)				
Isoniazid (300 mg/d) ×36 wk		Contact with active TB case: 2303 (69.2) Recent TST conversion 937 (28.1) Fibrosis: 90 (2.7)	Median, 37	1782 (53.5)				
Thompson et al,[97] 1982 (IUAT) (n = 27 830 participants)	Age 20-64 y with fibrotic pulmonary lesions not previously treated with anti-TB medications; race/ethnicity NR BCG vaccination NR[f,g]	NR	Median, 50; 38% were 55-65 y	NR (53)	5 y	Yes (≥6 mm Mantoux test)[h]	7 European countries (low and intermediate)[i]	Good (for KQ3) Fair (for KQ5)
Isoniazid (300 mg/d) ×12 wk								
Isoniazid (300 mg/d) ×24 wk								
Isoniazid (300 mg/d) ×52 wk								
Placebo								

(continued)

Table 2. Study Characteristics of Randomized Clinical Trials of Benefits (Key Question 3) and Harms (Key Question 5) of Treatment (continued)

Source	Population	TB Risk Factors, No. (%)	Age, y	Men, No. (%)	Follow-up	LTBI Confirmed	Country (TB Burden)[a]	Quality[b]
White et al,[98] 2012 (n = 364 participants)	Inmates ≥18 y diagnosed with LTBI at San Francisco jail entry; 334 (92%) nonwhite BCG vaccination NR	Foreign-born: 278 (76) Jailed before: 255 (70) Drug/alcohol problem: 186 (51)	<35: 258 (71%) ≥35: 106 (29%)			Yes (method NR)	United States (low)	Fair
Rifampin (600 mg/d) ×4 to 6 mo				166 (92)	16-24 wk			
Isoniazid (900 mg twice a wk) ×9 to 12 mo				173 (94)	36-52 wk			

Abbreviations: HIV, human immunodeficiency virus; IGRA, interferon-gamma release assays; IUAT, International Union Against Tuberculosis and Lung Disease; LTBI, latent tuberculosis infection; NR, not reported; TB, tuberculosis; TST, tuberculin skin test.

[a] Tuberculosis burden per 100 000 according to World Health Organization classification: low, <10 cases; intermediate, 10-99 cases; high, >100 cases.

[b] Quality assessed using criteria developed by the US Preventive Services Task Force.

[c] Number of participants who have been in close contact with an individual with active tuberculosis unspecified.

[d] Although tuberculosis burden in Canada is low, 54%-55% of the Canadian participants (n = 462) were born in countries with high tuberculosis incidence.

[e] Data extracted from supplemental data (P. LoBue, MD, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, written communication) for eligible study subgroup (HIV-negative participants with TST or IGRA confirmation).

[f] Inclusion criteria initially limited to ages 20-64 years, but a few persons are included outside these limits.

[g] Fibrotic pulmonary lesions defined as well-delineated radiographic lesions of probable tuberculous origin, usually in the upper half of the lung, which had been stable during the year prior to entry. For participants, the lesions had been known to exist for a median of 8 years (range, 11 months to 58 years).

[h] Median induration was 15 mm (range, 6-90 mm).

[i] Czechoslovakia (low), Finland (low), Germany (low), Hungary (intermediate), Poland (intermediate), Romania (intermediate), Yugoslavia (low-intermediate).

Three studies provided evidence on harms of rifampin as compared with isoniazid. One open-label RCT conducted in Canada (n = 116) compared 4 months of rifampin with 9 months of isoniazid.[94] A later study by the same authors (described above) randomized 847 participants to the same 2 treatments.[95] Participants in both studies were 18 years or older with documented LTBI. The third trial randomized inmates (n = 365) in the San Francisco City and County Jail with LTBI at jail entry to 9 months of isoniazid or 4 months of rifampin.[98]

Rates of hepatotoxicity in these 3 RCTs among individuals receiving isoniazid were 5.2%,[94] 3.7%,[95] and 11.4%,[98] respectively. Rates among rifampin-treated patients were lower (0.0%, 0.7%, and 4.4%, respectively). Pooled estimates from these 3 RCTs found a greater risk of hepatotoxicity for patients treated with isoniazid than for those treated with rifampin (RR, 3.29 [95% CI, 1.72-6.28] [3 studies, 1327 participants]) (eFigure 5 in the Supplement). All studies reported zero deaths from hepatotoxicity. Rates of discontinuations because of adverse events were 13.8% (isoniazid) and 3.4% (rifampin)[94]; 5.6% (isoniazid) and 3.8% (rifampin)[95]; and 0.0% (isoniazid) and 1.1% (rifampin).[98] The pooled estimate found no statistically significant difference between treatments (RR, 1.61 [95% CI, 0.57-4.57] [3 studies; n = 1327]). Similar rates of gastrointestinal adverse events were reported among the 3 studies; various other harms were reported, but no significant differences between isoniazid and rifampin were identified.

The PREVENT TB trial (described above) reported rates of grade 3 hepatotoxicity of 4.9% in the rifapentine plus isoniazid group and 5.5% in the isoniazid-only group; corresponding rates of grade 4 hepatotoxicity were 1.0% and 1.1%, respectively.[96] The RR for grade 3 or 4 hepatotoxicity was 0.90 (95% CI, 0.75-1.08). Mortality from hepatotoxicity was reported in 1.0% of patients receiving isoniazid and 0.8% of patients receiving rifapentine plus isoniazid (RR, 0.83 [95% CI, 0.51-1.35]). Rates of discontinuation because of adverse events were 5.2% in the rifapentine plus isoniazid group and 4.1% in the isoniazid-only group. The RR of treatment discontinuation because of adverse events for rifapentine plus isoniazid vs isoniazid only was 1.28 (95% CI, 1.03-1.59). Possible hypersensitivity was reported in 0.5% of patients receiving isoniazid and 4.1% of patients receiving rifapentine plus isoniazid. The relative risk of possible hypersensitivity for rifapentine plus isoniazid vs isoniazid only was 8.04 (95% CI, 4.88-13.26).

Discussion

Table 3 summarizes the evidence reviewed to inform an updated USPSTF recommendation on screening for LTBI within primary care settings. For the populations and settings evaluated, currently available screening tests were moderately sensitive and, in countries with low TB burden , highly specific. Treatment with current CDC-recommended pharmacotherapy regimens was effective at reducing the progression to active TB, but treatment was associated with an increased risk for hepatotoxicity.

The applicability of the evidence on accuracy and reliability of screening tests to primary care practice settings and populations is uncertain for several reasons. The lack of a direct test for LTBI requires test accuracy studies to be performed in specific, nonprimary care–related populations (ie, active, confirmed TB for sensitivity;

Table 3. Summary of Evidence: Screening and Treatment for Latent Tuberculosis Infection in Adults

Key Question	No. of Studies	No. of Participants	Study Design	Summary of Findings (Including Consistency and Precision)	Applicability	Limitations (Including Reporting Bias)	Quality of Evidence
Key question 1: Benefits of screening	0	NA	NA	No studies evaluated the direct benefit of screening vs no screening.	NA	NA	NA
Key question 2: Accuracy of screening with TST	27[a]	11 083[b]	Observational studies assessing test accuracy	Sensitivity for detecting infection, 0.52 using 15-mm threshold to 0.79 for both the 5-mm and 10-mm thresholds; findings were mostly consistent but imprecise. Specificity 0.95-0.99 for all thresholds in low TB-burden countries, and findings were both consistent and precise.	TST using Mantoux procedure with intermediate-strength dose of PPD. Lack of direct test for LTBI requires extrapolation of test characteristics from participants with active TB (for sensitivity) and healthy, low-risk participants (for specificity).	Description of subject characteristics highly variable across studies. Independent interpretation of test often not reported. No evidence of reporting bias.	Fair
Key question 2: Accuracy of screening with IGRA	56[a]	6358[b]	Observational studies assessing test accuracy	Sensitivity for detecting infection, 0.77 to 0.90 depending on assay used; findings were consistent and precise. Specificity 0.95-0.98 depending on assay used; findings were consistent and precise in low TB-burden countries.	IGRAs require proper specimen handling prior to assay. FDA-approved threshold for positive T-SPOT.*TB* IGRA test used in US studies higher than threshold used in non-US studies. Findings from QuantiFERON IGRAs reflect several generations of the assay, some of which may no longer be commercially available. Lack of direct test for LTBI requires extrapolation of test characteristics from participants with active TB (for sensitivity) and healthy, low-risk participants (for specificity).	Description of participant characteristics and reporting of indeterminate results highly variable across studies. Independent interpretation of test often not reported. No evidence of reporting bias.	Fair
Key question 3: Benefits of treatment	3[c] (4 more in sensitivity analysis)	35 563[c] (8993 more in sensitivity analysis)	RCTs	IUAT trial found that isoniazid for 24 wk reduced the risk of developing active TB vs placebo (RR, 0.35 at 5 y [95% CI, 0.24-0.52]; NNT, 112)[d]. Data from 1 large open-label noninferiority trial[e] found that rifapentine + isoniazid was noninferior to isoniazid alone. Overall, trials reported limited data on deaths due to TB.	Isoniazid vs placebo: IUAT trial included participants with fibrotic pulmonary lesions and ≥6 mm TST. IUAT trial and RCTs used in sensitivity analyses[f] published >30 y ago. Rifapentine + isoniazid vs isoniazid alone: rifapentine + isoniazid was directly observed once weekly for 3 mo; most participants had a close contact with active TB; 25% were included because of recent TST conversion.	Isoniazid vs placebo: Studies in sensitivity analysis used longer duration (1 y),[g] and some used doses lower or higher than currently recommended. Rifapentine + isoniazid vs isoniazid alone: open label; single study. No evidence of reporting bias.	Good (fair to good for studies in sensitivity analysis)
Key question 4: Harms of screening	0	NA	NA	No studies were identified that evaluated the harms of screening vs no screening.	NA	NA	NA

(continued)

Table 3. Summary of Evidence: Screening and Treatment for Latent Tuberculosis Infection in Adults (continued)

Key Question	No. of Studies	No. of Participants	Study Design	Summary of Findings (Including Consistency and Precision)	Applicability	Limitations (Including Reporting Bias)	Quality of Evidence
Key question 5: Harms of treatment	5[h] (3 more in sensitivity analysis)	36 043[h] (7331 more in sensitivity analyses)	RCTs	Isoniazid vs placebo: IUAT trial found isoniazid for 24 wk increased risk of hepatotoxicity (RR, 4.59 at 5 y [95% CI, 2.03-10.39], NNH, 279)[i] and risk of GI adverse events (RR, 1.33 [95% CI, 1.01-1.75]) vs placebo. Hepatotoxicity: 0.14 deaths/1000 receiving isoniazid (RR, 2.35 [95% CI, 0.12-45.46]).[j] Isoniazid vs rifampin: consistent findings that risk of hepatotoxicity greater with isoniazid than with rifampin (pooled RR from 3 RCTs, 3.29 [95% CI, 1.72-6.28]). Rifapentine + isoniazid vs isoniazid alone: data from 1 noninferiority trial[e] found RR of 0.90 (95% CI, 0.75-1.08) for hepatotoxicity and increased risk of possible hypersensitivity with rifapentine + isoniazid (RR, 8.04 [95% CI, 4.88-13.26]).	Isoniazid vs placebo: IUAT trial included participants with fibrotic pulmonary lesions and ≥6-mm TST. IUAT trial and RCTs used in sensitivity analyses[k] published >30 y ago. Isoniazid vs rifampin: participants had positive TST in 2 trials; the other trial included inmates diagnosed with LTBI at jail entry. Rifapentine + isoniazid vs isoniazid alone: rifapentine + isoniazid was directly observed once weekly for 3 mo; most participants had a close contact with active TB; 25% were included because of recent TST conversion.	Isoniazid vs placebo: Harm ascertainment techniques not well described; very few deaths due to hepatotoxicity (rare events). Isoniazid vs rifampin: 2 trials were open-label, 1 trial had high attrition. Rifapentine + isoniazid vs isoniazid alone: open label; single study; high overall attrition. No evidence of reporting bias.	Fair

Abbreviations: FDA, US Food and Drug Administration; GI, gastrointestinal; IGRA, interferon-gamma release assay; IUAT, International Union Against Tuberculosis; LTBI, latent tuberculosis infection; NA, not applicable; NNH, number needed to harm; NNT, number needed to treat; PPD, purified protein derivative; RCT, randomized clinical trial; RR, relative risk; TST, tuberculin skin test.

[a] Unique studies contributing to estimates of sensitivity or specificity or both.

[b] Unique participants analyzed to generate estimates of sensitivity or specificity. Some studies analyzed the same participants in evaluation of different test thresholds.

[c] Includes 27 830 from the IUAT trial of isoniazid vs placebo, 847 from an RCT of isoniazid vs rifampin, and 6886 from trial of rifapentine + isoniazid vs isoniazid alone. In the IUAT trial, the only trial meeting all eligibility criteria for Key Question 3 that compared isoniazid with placebo, 6965 of the participants were treated with a Centers for Disease Control and Prevention (CDC)–approved regimen (isoniazid, 300 mg ×24 weeks).

[d] Data shown are based on the IUAT trial. The relative risks for the other IUAT treatment groups for developing active TB compared with placebo were 0.79 (95% CI, 0.58-1.06) for 12 weeks of isoniazid and 0.25 (95% CI, 0.16-0.39) for 52 weeks of isoniazid. Our sensitivity analysis including the IUAT trial plus 4 additional RCTs with follow-up ranging from 2 to 10 years found a similar risk (pooled RR, 0.31 [95% CI, 0.24-0.41]). Trials used in the sensitivity analysis were consistent (I^2 = 0%) and precise.

[e] Data from 1 open-label noninferiority trial that randomized 7731 individuals; we obtained data from the CDC for this table on the subset of participants most directly relevant for this review: the 6886 adults (≥18 years) who were HIV negative and were TST or IGRA positive. Findings were reasonably precise; consistency was not applicable (single study).

[f] Trials in sensitivity analysis enrolled household contacts of persons with active TB, veterans with inactive pulmonary TB, individuals residing in mental institutions, and military members exposed to persons with active TB.

[g] No longer a CDC-recommended treatment regimen.

[h] Includes 27 830 from the IUAT trial of isoniazid vs placebo, 1327 from 3 trials of isoniazid vs rifampin, and 6886 from a trial of rifapentine + isoniazid vs isoniazid alone.

[i] Data shown are based on the IUAT trial; our sensitivity analysis including the IUAT trial plus 3 additional RCTs found a similar risk (pooled RR, 5.04 [95% CI, 2.50-10.15], I^2 = 0%); pooled estimate includes combined data from all 3 isoniazid study groups (12 weeks, 24 weeks, 52 weeks) in the IUAT trial. Trials used in the sensitivity analysis were consistent, but overall pooled estimate was imprecise.

[j] There were 0 deaths due to hepatotoxicity in the IUAT trial placebo group. One additional RCT used in sensitivity analysis for this outcome reported 0 deaths from hepatotoxicity in either the isoniazid or placebo group.

[k] Trials in sensitivity analysis enrolled employees in a US hospital, individuals meeting American Thoracic Society criteria referred to a US military medical center, and veterans with inactive pulmonary TB.

healthy populations with low TB risk for specificity). Estimates for specificity were lower in studies conducted with populations from countries with intermediate TB burden, specifically Turkey and South Korea. This could be the result of unintentional inclusion of participants with unknown past TB exposure, inclusion of BCG-vaccinated participants, or other factors that affect the administration or interpretation of tests in these countries. The studies of screening tests in this review did not consistently report comorbidities of the study population tested, and although studies from populations with more than 25% HIV-infected individuals were excluded, patients with active TB often have underlying comorbidities related to immunosuppression. The extent to which sensitivity of tests is blunted by this underlying immunosuppression is not known and may result in lower estimates for sensitivity than would be found in populations with latent infection. Conversely, the presence of active TB disease may result in more host sensitization, so this population may overestimate the true sensitivity of the tests for latent infection. Although 7 studies for KQ2 may have included 15-, 16-, and 17-year-olds,[26,34,35,42,67,70,77] the scope of this review did not include children and adolescents, and so findings should not be generalized to this population.

The evidence on effectiveness of treatment for LTBI comes primarily from the IUAT trial. It enrolled participants with pulmonary fibrotic lesions, a group thought to be at the highest risk for progression to active TB. It also found that individuals with smaller lesions progressed to active TB at lower rates than those with larger lesions. Thus, estimates of treatment effectiveness may represent the upper bounds of effectiveness, and effectiveness may be lower in other populations. The evidence on harms suggests an RR of 4.59 for hepatotoxicity with 6 months of isoniazid compared with placebo and an RR of 3.29 compared with rifampin. Deaths because of hepatotoxicity were rare across all studies, so estimates were imprecise. In the IUAT study, all 3 participants who died of hepatitis had continued to take isoniazid after liver abnormalities were recognized.[97] The rate of treatment discontinuation because of adverse events was modestly increased for isoniazid compared with placebo based on a single study but was no different between isoniazid and rifampin based on a pooled estimate from a 3-study body of evidence that was somewhat inconsistent and imprecise.

Isoniazid was established as an effective treatment of LTBI several decades ago, and CDC treatment recommendations have evolved based on studies comparing shorter durations and alternative regimens against the standard isoniazid regimen to reduce harms, improve adherence, or both, rather than to assess efficacy. Given that treatment of LTBI has been the standard of care for decades, contemporary data for estimating efficacy or effectiveness among untreated populations are not available. Furthermore, over time the prevalence of active TB has declined, yet the prevalence of resistant strains among those infected has increased. Thus, the applicability of treatment evidence from before the current era is unclear. In addition, proponents for screening suggest benefits on outcomes related to TB transmission and through case-finding of active TB that occurs during screening. However, no studies meeting eligibility criteria that reported these outcomes were identified.

This review had several limitations. A substantial amount of statistical heterogeneity was identified in some of the pooled estimates of test accuracy; however, this heterogeneity is unlikely to be clinically relevant and can be explained by the number of included studies with large sample sizes and precise estimates, a phenomenon that has been described as producing elevated I^2 estimates.[99,100] The review excluded treatments not recommended by the CDC and also excluded several populations at highest risk of TB (eg, individuals with HIV), as the scope of the review was limited to generally healthy adults in primary care settings. Although the scope of the review was narrow, the findings are consistent with those from several other reviews of test characteristics and treatment that included broader populations and settings.[101-105]

Conclusions

No studies evaluated the benefits and harms of screening compared with no screening. Both the TST and IGRAs are moderately sensitive and highly specific within countries with low TB burden. Treatment reduced the risk of active TB among the populations included in this review. Isoniazid is associated with higher rates of hepatotoxicity than placebo or rifampin.

ARTICLE INFORMATION

Author Contributions: Dr Kahwati had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Kahwati, Feltner, Halpern, Jonas.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kahwati, Halpern, Boland, Jonas.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kahwati, Halpern, Amick, Jonas.
Obtained funding: Feltner, Woodell, Jonas.
Administrative, technical, or material support: Feltner, Woodell, Boland, Amick, Weber.
Study supervision: Kahwati, Feltner, Halpern, Jonas.

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