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Screening for Latent Tuberculosis Infection in Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Latent tuberculosis infection (LTBI) can progress to active tuberculosis disease, causing morbidity and mortality.

OBJECTIVE To review the evidence on benefits and harms of screening for and treatment of LTBI in adults to inform the US Preventive Services Task Force (USPSTF).

DATA SOURCES PubMed/MEDLINE, Cochrane Library, and trial registries through December 3, 2021; references; experts; literature surveillance through January 20, 2023.

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

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality; qualitative synthesis of findings; meta-analyses conducted when a sufficient number of similar studies were available.

MAIN OUTCOMES AND MEASURES Screening test accuracy; development of active tuberculosis disease, transmission, quality of life, mortality, and harms.

RESULTS A total of 113 publications were included (112 studies; N = 69 009). No studies directly evaluated the benefits and harms of screening. Pooled estimates for sensitivity of the TST were 0.80 (95% CI, 0.74-0.87) at the 5-mm induration threshold, 0.81 (95% CI, 0.76-0.87) at the 10-mm threshold, and 0.60 (95% CI, 0.46-0.74) at the 15-mm threshold. Pooled estimates for sensitivity of IGRA tests ranged from 0.81 (95% CI, 0.79-0.84) to 0.90 (95% CI, 0.87-0.92). 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 clinical trial found a relative risk (RR) for progression to active tuberculosis at 5 years of 0.35 (95% CI, 0.24-0.52) for 24 weeks of isoniazid compared with placebo (number needed to treat, 112) and an increase in hepatotoxicity (RR, 4.59 [95% CI, 2.03-10.39]; number needed to harm, 279). A previously published meta-analysis reported that multiple regimens were efficacious compared with placebo or no treatment. Meta-analysis found greater risk for hepatotoxicity with isoniazid than with rifampin (pooled RR, 4.22 [95% CI, 2.21-8.06]; n = 7339).

CONCLUSIONS AND RELEVANCE No studies directly evaluated the benefits and harms of screening for LTBI compared with no screening. TST and IGRAs were moderately sensitive and highly specific. Treatment of LTBI with recommended regimens reduced the risk of progression to active tuberculosis. Isoniazid was associated with higher rates of hepatotoxicity than placebo or rifampin.

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Tuberculosis is a substantial health issue globally, with approximately 10 million cases of active tuberculosis and 1.5 million tuberculosis-related deaths worldwide in 2020.[1,2] In the US, active tuberculosis is a more limited health problem, with cases declining in recent decades. In 2019, 8904 new active tuberculosis cases were reported in the US, corresponding to an incidence rate of 2.7 cases per 100 000 population.[3] There were 526 deaths from tuberculosis disease in the US in 2019.[4] In 2020 in the US, 5127 active tuberculosis 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 2018 cases and a rate of 0.7 cases per 100 000 population among US-born persons.[5]

Estimating the prevalence of latent tuberculosis infection (LTBI) in the US is challenging because no direct test exists, and reporting of latent infection is not required by the Centers for Disease Control and Prevention (CDC) National Notifiable Disease Surveillance System.[6,7] US national data from the National Health and Nutrition Examination Survey suggest a population prevalence for LTBI of approximately 5% (95% CI, 4.2-5.8) for US-born persons and 15.9% (95% CI, 13.5-18.7) among persons born outside the US based on interferon-gamma release assay (IGRA) alone.[8]

In developed countries with a low prevalence of tuberculosis such as the US, many groups, including the CDC, recommend that LTBI screening be performed among high-risk groups and when treatment is feasible (eBackground and eTable 1 in the Supplement). The tuberculin skin test (TST) and IGRAs are screening tests available for LTBI. If screening test results 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 tuberculosis disease (because screening tests alone cannot differentiate LTBI from tuberculosis disease) prior to confirming the diagnosis of LTBI and offering preventive medication (eTable 2 in the Supplement).

In 2016, the US Preventive Services Task Force (USPSTF) recommended screening for LTBI in asymptomatic adults at increased risk (B recommendation). This updated review evaluates the current evidence on benefits and harms of screening for and treatment of LTBI in settings and populations relevant to US primary care to inform an updated recommendation by the USPSTF.

Methods

Scope of the Review

Figure 1 shows the analytic framework and key questions (KQs) that guided the review. Detailed methods and additional details about results (eg, for screening test reliability, for harms other than hepatotoxicity, for trials comparing rifampin plus isoniazid with rifapentine plus isoniazid) are available in the full evidence report.[10] In addition to addressing the KQs, this review looked for evidence related to 1 contextual question that focused on risk assessment tools available for use in primary care to identify adults to screen for LTBI. Literature addressing the contextual question is summarized in eMethods 1 in the Supplement.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published from January 30, 2015, through December 3, 2021 (eMethods 2 in the Supplement). To supplement electronic searches, investigators reviewed reference lists of pertinent articles, studies suggested by reviewers, and comments received during public commenting periods. Since December 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 January 20, 2023. No additional studies were identified.

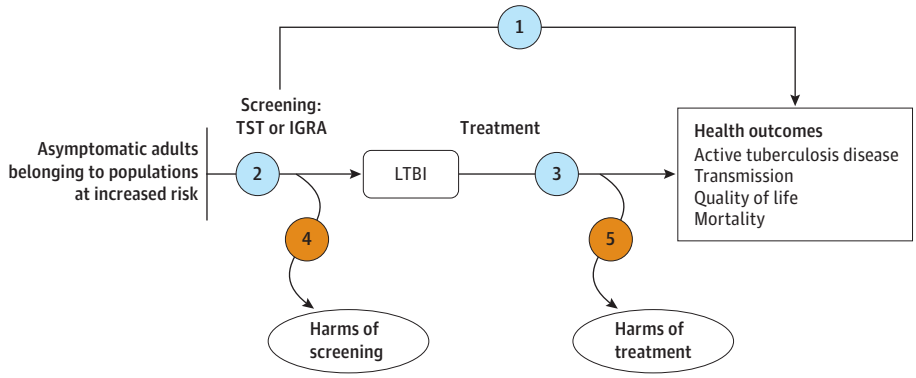
Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified eligibility criteria (eMethods 3 in the Supplement). Disagreements were resolved by discussion and consensus. In addition to studies identified in the update searches, studies included in the previous review for the USPSTF were reassessed for eligibility. Relevant English-language studies of good or fair quality were eligible. Except for KQ2 (on test accuracy), only studies conducted in settings considered to be applicable to primary care and conducted in countries categorized as "very high" or "high" on the United Nations Human Development Index were eligible. Study settings considered applicable to primary care included homeless shelters, correctional facilities, college health settings, long-term care facilities, and public health clinics. Studies were excluded if more than 25% of the study population was younger than 18 years or known to be HIV-positive, unless results were stratified by these characteristics.

For KQ1, randomized clinical trials (RCTs) or prospective cohort studies were eligible if they focused on asymptomatic adults belonging to populations at increased risk for developing active tuberculosis (eg, 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 tuberculosis prevalence, and persons who work with such individuals). Studies of close contacts of persons with active tuberculosis were not eligible because testing and treatment of such populations is considered part of contact tracing for public health. Studies of persons with underlying immunosuppression and for whom LTBI screening and treatment would be part of standard disease management were also excluded (eg, persons with HIV, head and neck cancer, leukemia or lymphoma, silicosis, history of organ transplant or planned organ transplant, planned or active use of tumor necrosis factor inhibitors, and planned or active use of chemotherapy).

For screening test accuracy (KQ2), sensitivity data were from studies of persons with bacteriologically confirmed, active tuberculosis who had not yet received treatment (or who had received no more than a few weeks of treatment) and specificity data were from studies of healthy participants known to be at low risk for tuberculosis and free of tuberculosis exposure. Studies were eligible that evaluated the TST using the Mantoux method with use of standard induration thresholds for a positive test result (ie, 5 mm, 10 mm, or 15 mm) or 3 commercially available IGRAs (T-SPOT.*TB* [Oxford Immunotec Global], QuantiFERON-TB Gold In-Tube [QFT-GIT; Qiagen; third-generation test], and QuantiFERON-TB Gold Plus [QFT-Gold Plus; Qiagen; fourth-generation test]). For KQ2, studies of test-retest, interrater, and interlaboratory reliability

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



Key questions

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, including among specific populations of interest?

2. Accuracy and reliability of screening
   a. What are the accuracy and reliability of the TST or IGRA for screening in asymptomatic adults who are at increased risk for developing active tuberculosis disease, including among specific populations of interest?
   b. 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 tuberculosis disease, including among specific populations of interest?

3. What are the benefits of treatment for LTBI with CDC-recommended pharmacotherapy regimens, including among specific populations of interest?

4. Harms of screening
   a. Are harms associated with screening for LTBI, including among specific populations of interest?
   b. Do these harms differ by screening method or strategy?
   c. 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?

Contextual question

CQ1 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?

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. For additional information see the USPSTF Procedure Manual.[9] CDC indicates Centers for Disease Control and Prevention; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

were also eligible. For KQ3 and KQ5, 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 were eligible.

For 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. For KQ5, prospective cohort studies and case-control studies were also eligible.

Data Extraction and Quality Assessment

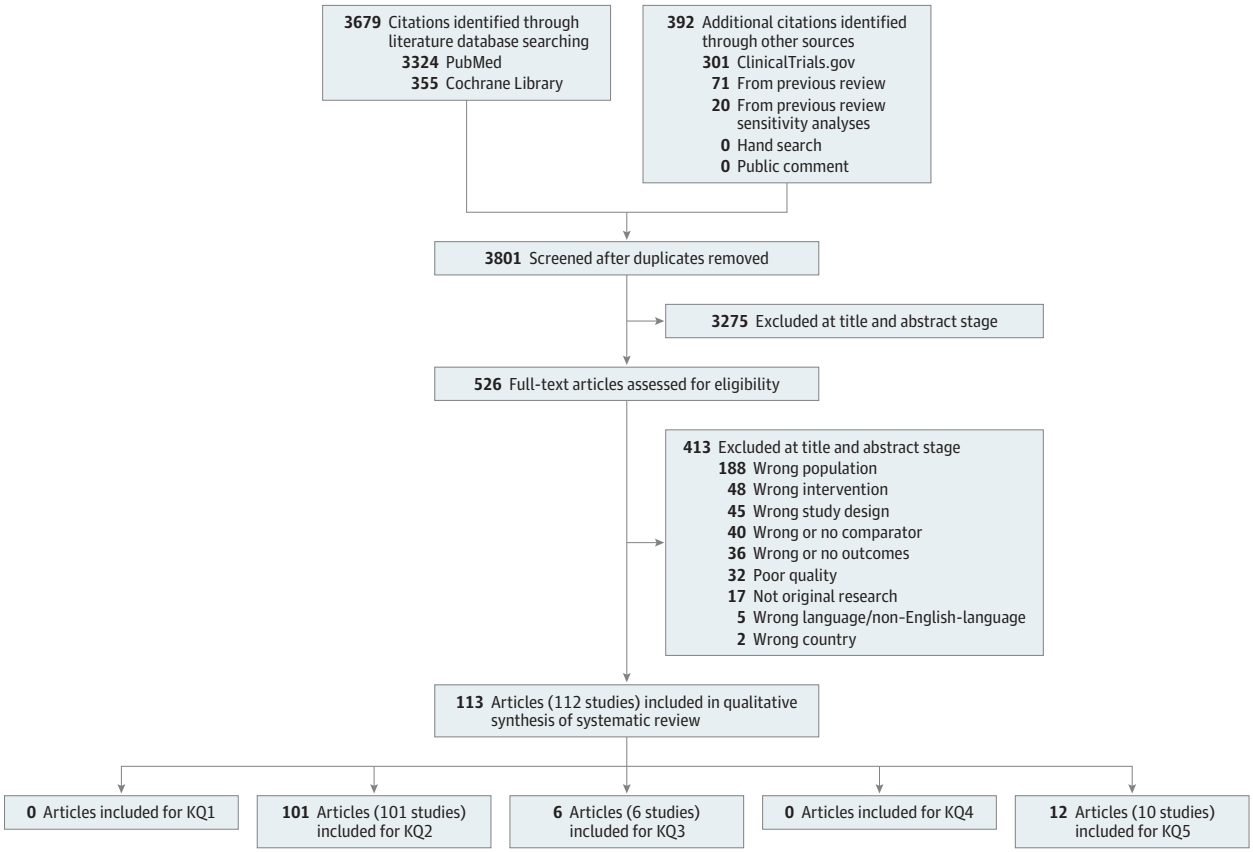
For each included study, 1 investigator extracted pertinent information about populations, tests or interventions, comparators, outcomes, settings, and designs, and a second investigator reviewed the information for completeness and accuracy. Two investigators independently assessed each study's methodological quality as good, fair, or poor using predefined criteria developed by the USPSTF and adapted for this topic and from validated tools for assessing risk of bias (eMethods 4 in the Supplement).[9,11,12] Disagreements were resolved by discussion. Quality ratings for individual studies are provided in eTables 3 through 9 in the Supplement.

Data Synthesis and Analysis

Findings for each KQ were summarized in tabular and narrative format. The overall strength of the evidence for each KQ was assessed 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 Evidence-based Practice Center program).[9] Additionally, the applicability of the findings to US primary care populations and settings was assessed. Discrepancies were resolved through consensus discussion.

To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity of the studies was assessed according to established guidance.[13] When at least 3 similar

Figure 2. Literature Search Flow Diagram: Screening for Latent Tuberculosis Infection in Adults



The sum of the number of studies per key question (KQ) exceeds the total number of studies because some studies were applicable to multiple KQs.

studies were available, quantitative syntheses were conducted using random-effects models with the inverse-variance weighted method of DerSimonian and Laird to generate pooled estimates.[14]

For screening test accuracy (KQ2), separate pooled estimates of proportions were generated for sensitivity and specificity because these accuracy data were collected from independent samples.[15] Pooled estimates were generated for test accuracy stratified by potentially important covariates such as country tuberculosis burden, prevalence of BCG vaccination in the study population, timing of testing with respect to the initiation of pharmacotherapy, and prevalence of persons with HIV infection. For KQ2, statistical heterogeneity was assessed through visual inspection of the forest plots because the I^2 statistic has limitations when used for evaluating heterogeneity in diagnostic accuracy studies.[16,17]

For KQ3 and KQ5, statistical heterogeneity was also assessed using the I^2 statistic when pooled estimates were available. 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. For benefits and harms of treatment (KQ3 and KQ5), sensitivity analyses were conducted by adding RCTs that were either poor quality, did not meet all of the inclusion criteria (eg, they used longer duration of treatment or different doses than currently recommended), or both. All quantitative analyses were conducted using Stata version 17 (StataCorp).

Results

Investigators identified 3801 unique records and assessed 526 full-text articles for eligibility (**Figure 2**). A total of 112 studies (113 articles) with 69 009 participants were included.

Benefits of Screening

Key Question 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, including among specific populations of interest?

No eligible studies were identified.

Screening Accuracy

Key Question 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 tuberculosis disease, including among specific populations of interest?

The review identified 101 studies of good or fair quality assessing the sensitivity, specificity, or reliability of 1 or more of the included screening tests. Thirty-two studies reported on TST (eTables 10 and 12 in the Supplement).[18-49] Among studies of IGRAs, 39 reported on T-SPOT.*TB*,[19,37-39,43,46,48,50-81] 12 reported

Table 1. Summary of Sensitivity and Specificity Estimates for Various Thresholds of the TST and IGRA Tests

Test	Sensitivity			Specificity		
	No. of studies (total No.)	Pooled estimate (95% CI)	I^2, %	No. of studies (total No.)	Pooled estimate (95% CI)	I^2, %
TST induration threshold						
5 mm	12 (1323)	0.80 (0.74-0.87)	94.2	3 (5149)	0.95 (0.94-0.97)	NA[a]
10 mm	15 (1427)	0.81 (0.76-0.87)	91.4	8 (9604)	0.98 (0.97-0.99)	96.2
15 mm	9 (1004)	0.60 (0.46-0.74)	96.5	10 (9563)	0.99 (0.98-0.99)	88.7
IGRA						
T-SPOT.*TB*	37 (5367)	0.90 (0.87-0.92)	93.2	2 (1664)	0.95 (0.91-0.97)[b]	NA[a]
					0.97 (0.96-0.98)[b]	
QFT-GIT	48 (7055)	0.81 (0.79-0.84)	89.9	3 (2090)	0.99 (0.98-0.99)	NA[a]
QFT-Plus	11 (939)	0.89 (0.84-0.94)	87.9	1 (211)	0.98 (0.95-0.99)[b]	NA[a]

Abbreviations: IGRA, interferon-gamma release assay; NA, not applicable; QFT-GIT, QuantiFERON-TB Gold In-Tube (third-generation test); QFT-Plus, QuantiFERON-TB Gold Plus (fourth-generation test); T-SPOT.*TB*, commercial ELISPOT assay; TST, tuberculin skin test.

[a] I^2 was not calculated when fewer than 4 studies were available.

[b] Fewer than 3 studies were available, so we did not conduct a quantitative synthesis.

on QFT-Gold Plus,[70,71,80-90] and 51 reported on QFT-GIT (eTables 11 and 13 in the Supplement).[18, 19, 23, 25, 31, 36, 41-44, 50, 54, 58, 63, 65, 67, 68, 70, 71, 79, 80, 82-87, 89, 91-113] Nineteen studies were conducted exclusively or partly in the US.[19-21, 24, 27, 29, 30, 32-34, 37, 45, 59, 82, 87, 105, 114-116] Pooled estimates for sensitivity and specificity of TST by induration threshold and of IGRAs by assay are summarized in **Table 1** (greater detail is provided in eFigures 1-29 in the Supplement). The pooled sensitivity for TST ranged from 0.60 to 0.81 across induration thresholds for a positive test result (ie, 5 mm, 10 mm, or 15 mm). The pooled sensitivity across IGRAs ranged from 0.81 to 0.90. The pooled specificity for all tests ranged from 0.95 to 0.99. No new studies were identified for this update that reported on the reliability of the various screening tests. The prior review on this topic for the USPSTF identified 9 relevant studies on reliability (eTable 14 and eResults in the Supplement).[19,32,33,39,114-118]

Key Question 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 tuberculosis disease, including among specific populations of interest?

No eligible studies were identified.

Benefits of Treatment

Key Question 3. What are the benefits of treatment for LTBI with CDC–recommended pharmacotherapy regimens, including among specific populations of interest?

Five RCTs (eTable 15 in the Supplement) and 1 network meta-analysis were included.[119-124] One RCT compared isoniazid with placebo, 2 compared rifampin with isoniazid, and 2 compared rifapentine plus isoniazid with isoniazid alone. Two of the articles describing RCTs[121,123] and the network meta-analysis[124] were new in this update. Four additional RCTs[125-128] that compared isoniazid with placebo that did not meet all eligibility criteria were used in sensitivity analyses (eTable 16 in the Supplement).

Isoniazid Compared With Placebo

The International Union Against Tuberculosis (IUAT) trial[119] randomized 27 830 adults with fibrotic pulmonary lesions and a TST induration of 6 mm or larger, but not active tuberculosis or previous antituberculosis treatment, to 4 groups: isoniazid (300 mg daily for 12 weeks), isoniazid (300 mg daily for 24 weeks), isoniazid (300 mg daily for 52 weeks), or placebo. The median age was 50 years. After 5 years of follow-up, 76 participants (1.1%) in the 12-week group, 34 (0.5%) in the 24-week group, 24 (0.3%) in the 52-week group, and 97 (1.4%) in the placebo group developed active tuberculosis (eTable 17 in the Supplement). The relative risks (RRs) for developing active tuberculosis compared with placebo were 0.79 (95% CI, 0.58-1.06) in the 12-week group, 0.35 (95% CI, 0.24-0.52) in the 24-week group, and 0.25 (95% CI, 0.16-0.39) in the 52-week group. For the 24-week CDC-recommended regimen (among the current CDC alternative regimens), the results indicated a number needed to treat of 112 to prevent 1 case of active tuberculosis. There were no deaths due to tuberculosis in any of the isoniazid groups; 3 persons died of tuberculosis in the placebo group. The sensitivity analyses using combined data from the 24- and 52-week groups from the IUAT trial and 4 additional RCTs, including a total of 36 823 participants, found an RR of 0.31 (95% CI, 0.24-0.41) for developing active tuberculosis compared with placebo and no statistical heterogeneity in effects between studies (I^2 = 0.0%) (eFigure 30 in the Supplement).

Rifampin Compared With Isoniazid

Two RCTs comparing rifampin with isoniazid were included. The first was an open-label, multinational trial that randomized 847 participants to 4 months of rifampin or 9 months of isoniazid to compare adverse events and treatment completion.[121] It reported 0 deaths from tuberculosis in either group and reported all-cause mortality with 0 deaths in the rifampin group and 1 in the isoniazid group. The second RCT was an open-label, multinational trial that randomized 6063 participants at increased risk of progression to active tuberculosis to 4 months of rifampin (now a CDC-preferred regimen, strong recommendation) or 9 months of isoniazid (now an alternative CDC regimen).[121] In the isoniazid group, 9 participants developed active tuberculosis compared with 8 in the rifampin group, and rifampin was found to be noninferior to isoniazid.

Rifapentine Plus Isoniazid Compared With Isoniazid Alone

Two RCTs compared rifapentine plus isoniazid with isoniazid alone. The PREVENT TB study was an open-label, multinational

noninferiority trial that randomized persons to directly observed once-weekly rifapentine plus isoniazid for 3 months or to daily self-administered isoniazid for 9 months.[122] Data were obtained from the CDC for the subset of participants most directly relevant for this review: the 6886 adults (aged ≥18 years) who were HIV negative and TST- or IGRA-positive. For this subset, active tuberculosis developed in 5 persons in the combination therapy group and in 10 persons in the isoniazid-only group, and combination therapy was found to be noninferior. Overall mortality was similar for the 2 groups (30 vs 34 deaths, respectively; $P = .42$). The second RCT was an open-label multicenter trial that randomized 283 participants to either 3 months of once-weekly, directly observed rifapentine plus isoniazid or 9 months of daily, directly observed isoniazid alone.[123] It reported 0 deaths from any cause in both groups.

Network Meta-analysis

The network meta-analysis (53 included studies) used a mixed-treatment comparison methodology and focused on 2 prespecified end points: prevention of active tuberculosis and hepatotoxicity.[124] It found that the shorter-duration recommended regimens are efficacious for preventing active tuberculosis (eg, rifampin for 3 to 4 months, rifapentine plus isoniazid combination, isoniazid for 6 months) and may have fewer adverse effects and higher completion rates. That analysis included studies among children; HIV-infected persons; household or close contacts of persons with active tuberculosis 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 this review. For prevention of active tuberculosis, it 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}, 0.50-0.83] vs placebo) or longer, 3- to 4-month regimens of rifampin plus isonizid (OR, 0.53 [95% CrI, 0.36-0.78] vs placebo), and weekly regimens of rifapentine plus isoniazid (OR, 0.36 [95% CrI, 0.18-0.73] vs no treatment).

No studies reported benefits related to quality of life or tuberculosis transmission.

Harms of Screening

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

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

Key Question 4c. Do these harms differ by population?

No eligible studies were identified.

Harms of Treatment

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

Nine RCTs (described in 11 articles) and 1 network meta-analysis assessing harms associated with the treatment of LTBI were included (eTables 15 and 18 in the Supplement).[119-124,129-134] Among the RCTs, 1 compared isoniazid with placebo,[119] 4 compared rifampin with isoniazid (although participants of the Menzies [2008] phase 2 trial were included in the Menzies [2018] phase 3 trial),[120,121,130,131] 2 compared rifapentine plus isoniazid with isoniazid alone,[123,132] 1 compared rifampin plus isoniazid with rifapentine plus isoniazid,[133] and 1 compared weekly rifapentine plus isoniazid with twice-weekly rifapentine plus isoniazid.[134] 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.[121,123,124,129,132-134] Additional RCTs that did not meet all eligibility criteria were used in sensitivity analyses for harms. The criteria for RCTs to be included in sensitivity analyses were the same as those described for KQ3.

Hepatotoxicity From Isoniazid

The IUAT trial reported rates of hepatotoxicity development (eTable 18 in the Supplement).[119] The RRs for developing hepatotoxicity associated with isoniazid compared with placebo were 3.45 (95% CI, 1.49-7.99) for 12 weeks of treatment (24 vs 7 events), 4.59 (95% CI, 2.03-10.39) for 24 weeks of treatment (32 vs 7 events), and 6.21 (95% CI, 2.79-13.79) for 52 weeks of treatment (43 vs 7 events) (eFigure 31 in the Supplement). For the study groups comparing the 24-week CDC-approved regimen with placebo (n = 13 955), the results indicate that 1 case of hepatotoxicity would result from treating 279 persons with isoniazid (ie, a number needed to harm [NNH] of 279). Sensitivity analyses for hepatotoxicity associated with isoniazid compared with placebo using data from the IUAT trial (3 treatment groups combined) and 3 additional RCTs, including a total of 35 161 participants, found an RR of 5.04 (95% CI, 2.50-10.15) (eFigure 32 in the Supplement).[135-137]

Regarding mortality from hepatotoxicity, the IUAT trial reported rates of 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. The study had 0 deaths from hepatotoxicity among placebo-treated patients. The authors reported that the mortality rate from hepatitis associated with isoniazid was 0.14 deaths per 1000 persons receiving isoniazid, for a calculated RR of 2.35 (95% CI, 0.12-45.46; NNH, 6947).

Treatment Discontinuation With Isoniazid

Rates of treatment discontinuation because of adverse events in the IUAT trial were presented only for all 3 isoniazid treatment groups combined. A total of 345 patients (1.8%) receiving isoniazid discontinued treatment because of adverse events, compared with 84 patients (1.2%) receiving placebo. The RR of discontinuation due to adverse events among patients treated with isoniazid vs placebo was 1.50 (95% CI, 1.18-1.89; 1 RCT; n = 27 830; NNH, 167). Our sensitivity analysis using data from the IUAT trial and 3 additional RCTs, including a total of 55 398 participants, found an RR of 1.58 (95% CI, 1.00-2.49) (eFigure 33 in the Supplement).[125,127,137] The IUAT trial reported that 1.2% of patients receiving isoniazid and 0.9% of patients receiving placebo discontinued treatment due to gastrointestinal distress (RR, 1.33 [95% CI, 1.01-1.75]).[138]

Rifampin Compared With Isoniazid

Four open-label RCTs and 1 post hoc safety analysis provided evidence on harms for rifampin compared with isoniazid.[120,121,129-131] All 4 RCTs presented hepatotoxicity data; 1 combined data with an earlier trial by the same authors. Rates of hepatotoxicity in these RCTs among patients receiving isoniazid were 5.2%,[130] 1.9%,[121] and 11.4%.[131] Rates of hepatotoxicity among rifampin-treated patients

were 0.0%, 0.3%, and 4.4%. Meta-analysis of 3 RCTs (total n = 7339) found a greater risk of hepatotoxicity for patients treated with isoniazid than for those treated with rifampin (RR, 4.22 [95% CI, 2.21-8.06]; I^2 = 28.7%) (eFigure 34 in the Supplement). All studies reported 0 deaths from hepatotoxicity.

Rates of discontinuation because of adverse events were reported in all 4 included RCTs, but 1 trial combined its data with the data from an earlier phase 2 study by the same author. Rates were 13.8% for isoniazid and 3.4% for rifampin,[130] 2.3% for isoniazid and 0.9% for rifampin,[121] and 0.0% for isoniazid and 1.1% for rifampin.[131] Meta-analysis found no statistically significant difference between treatments (RR, 2.25 [95% CI, 0.90-5.59]; I^2 = 35.2%; n = 7339) (eFigure 35 in the Supplement).

Rifapentine Compared With Isoniazid

Two RCTs reported harms for rifapentine plus isoniazid compared with isoniazid alone.[122,123,132] Rates of grade 3 and 4 hepatotoxicity in the PREVENT TB study were 4.9% and 1.0% in the rifapentine plus isoniazid group and 5.5% and 1.1% in the isoniazid-only group (RR, 0.90 [95% CI, 0.75-1.08]).[122] A post hoc analysis reported 17 cases of hepatotoxicity attributable to rifapentine plus isoniazid (0.43% of those who received rifapentine plus isoniazid) and 97 attributable to isoniazid (2.70% of those who received it) (RR, 0.16 [95% CI, 0.10-0.28]).[132] The second trial reported elevations of aspartate aminotransferase and alanine aminotransferase levels greater than 3 times the upper limit of normal in 4.5% of the rifapentine plus isoniazid group and in 9.9% in the isoniazid-alone group (RR, 0.46 [95% CI, 0.18-1.17]) and reported clinically relevant hepatotoxicity in 1.5% vs 5.3% (RR, 0.28 [95% CI, 0.06-1.34]).

Rates of discontinuation because of adverse events were higher in the rifapentine plus isoniazid groups in both studies (5.2% in PREVENT TB and 9.1% in the trial conducted in Taiwan) than in the isoniazid-only groups (4.1% and 5.3%) (RR, 1.28 [95% CI, 1.03-1.59] in PREVENT TB and RR, 1.70 [95% CI, 0.69-4.19] in the trial conducted in Taiwan). The studies evaluated various other harms, including possible hypersensitivity, systemic drug reactions, and flu-like symptoms, which occurred with greater frequency in the rifapentine plus isoniazid groups. Possible hypersensitivity was reported in 4.1% of patients receiving rifapentine plus isoniazid and 0.5% of patients receiving isoniazid only in the PREVENT TB study (RR, 8.04 [95% CI, 4.88-13.26]).[5]

Other Studies

A single RCT, the HALT LTBI pilot study, compared self-administered rifapentine plus isoniazid daily for 90 days with rifapentine plus isoniazid weekly for 12 weeks. That study was an open-label trial that randomized 52 participants with LTBI.[133] A single open-label RCT compared directly observed, once-weekly isoniazid up to 900 mg and rifapentine up to 900 mg for 12 weeks (the 3HP regimen), directly observed twice-weekly isoniazid up to 600 mg and rifapentine up to 600 mg for 8 weeks (the $2H_2P_2$ regimen), and an untreated control group.[134] Results for these trials did not contribute to main conclusions of the review and are available in the full evidence report.[10]

The included network meta-analysis found greater odds of hepatotoxicity with longer duration of therapy and regimens containing isoniazid only (isoniazid [6 months] vs no treatment: OR, 1.10 [95% CrI, 0.40-3.17]; isoniazid [9 months] vs no treatment: OR, 1.70 [95% CrI, 0.35-8.05]; isoniazid [12-72 months] vs no treatment: OR, 2.72 [95% CrI, 0.96-7.44]) than with other regimens currently recommended by the CDC (rifapentine plus isoniazid vs no treatment: 0.52 [95% CrI, 0.13-2.15]; rifampin [3-4 months] vs no treatment: OR, 0.14 [95% CrI, 0.02-0.81]; rifampin plus isoniazid [3-4 months] vs no treatment: 0.72 [95% CrI, 0.21-2.37]).[124] Although data on hepatotoxicity were limited, CrIs were wide (estimates were imprecise), and findings were based on relatively few events.

Discussion

This study reviewed the evidence on benefits and harms of screening for LTBI in adults. **Table 2** provides a summary of the main findings, including an assessment of the strength of evidence for each KQ, along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability.

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 a prior review for the USPSTF,[139] are generally consistent with these findings.[140-143] The applicability of this evidence to primary care practice settings and populations is somewhat uncertain because the lack of a direct test for LTBI requires extrapolation of accuracy from specific populations (eg, populations with active, confirmed tuberculosis for sensitivity; healthy persons without tuberculosis risks and exposures for specificity). Nevertheless, it seems reasonable to assume applicability to primary care practice settings that serve high-risk populations (eg, clinics serving persons who had temporary or permanent residence in a country with a high tuberculosis 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 latent infection to inform preventive treatment decisions.

The best evidence on effectiveness of pharmacotherapy with a CDC-recommended regimen vs placebo was from the IUAT trial (n = 27 830). That trial enrolled participants with pulmonary fibrotic lesions, a group thought to be at the highest risk for progression to active tuberculosis, and reported that participants with smaller lesions progressed to active tuberculosis at lower rates than those with larger lesions. In addition, the treatment studies used in the current 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,[125] veterans with inactive pulmonary tuberculosis,[126,135] persons residing in mental institutions,[127] and military members exposed to an active tuberculosis case.[128] Thus, the available evidence has uncertain applicability to persons in primary care settings who screen positive on the TST or IGRA but have normal findings on chest radiographs or who are not recent converters or close contacts. Therefore, estimates of treatment effectiveness may represent the upper bounds of effectiveness.

Regarding applicability of the evidence comparing isoniazid with placebo, the trials were published more than 40 years ago

Table 2. Summary of Evidence on Screening for and Treatment of LTBI in Adults

Topic	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
KQ1: Benefits of screening							
	0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ2: Accuracy of screening							
TST	31 studies of test accuracy (11 879)	5-mm induration: pooled sensitivity, 0.80 (95% CI, 0.74-0.87); 12 studies (1323 participants); pooled specificity, 0.95 (95% CI, 0.94-0.97); 3 studies (5149 participants) 10-mm induration: pooled sensitivity, 0.81 (95% CI, 0.76-0.87); 15 studies (1427 participants); pooled specificity, 0.98 (95% CI, 0.97-0.99); 8 studies (9604 participants) 15-mm induration: pooled sensitivity, 0.60 (95% CI, 0.46-0.74); 9 studies (1004 participants); pooled specificity, 0.99 (95% CI, 0.98-0.99); 10 studies (9563 participants)	Consistent but imprecise for sensitivity for 5 mm and 10 mm Inconsistent and imprecise for sensitivity for 15 mm Consistent and precise for specificity	Fair to good	Independent interpretation of test often not reported Description of participant characteristics highly variable across studies Reporting bias not detected	Moderate for sensitivity for 5 mm and 10 mm Low for sensitivity for 15 mm High for specificity	TST using Mantoux procedure with intermediate-strength dose of PPD Lack of direct test for LTBI requires extrapolation of test characteristics from active tuberculosis (sensitivity) and healthy, low-risk populations (specificity) The 15-mm threshold is not recommended in current practice for patients at high risk for tuberculosis infection
IGRA	79 studies of test accuracy (13 493)	T-SPOT.*TB*: pooled sensitivity, 0.90 (95% CI, 0.87-0.92); 37 studies (5367 participants); specificity from 2 studies (1664 participants): 0.95 (95% CI, 0.91-0.97) and 0.97 (95% CI, 0.96-0.98) QFT-GIT: Pooled sensitivity, 0.81 (95% CI, 0.79-0.84); 48 studies (7055 participants); pooled specificity, 0.99 (95% CI, 0.98-0.99); 3 studies (2090 participants) QFT-Plus: pooled sensitivity, 0.89 (95% CI, 0.84-0.94); 11 studies (939 participants); specificity, 0.98 (95% CI, 0.95-0.99); 1 study (211 participants)	Consistent and precise for sensitivity for all IGRAs For specificity, consistent and precise for T-SPOT.*TB* and QFT-GIT Consistency unknown (single study), precise for QFT-Plus	Fair to good for sensitivity for T-SPOT.*TB* and QFT-GIT Fair for QFT-Plus Fair for specificity for all IGRAs	Independent interpretation of test often not reported; description of participant characteristics highly variable across studies Studies varied with respect to how they reported borderline or indeterminate results Reporting bias not detected	High for sensitivity for T-SPOT.*TB* and QFT-GIT Moderate for QFT-Plus Moderate for specificity for T-SPOT.*TB* and QFT-GIT Low for QFT-Plus	Lack of direct test for LTBI requires extrapolation of test characteristics from active tuberculosis (sensitivity) and healthy, low-risk (specificity) populations IGRAs require proper specimen handling prior to assay
KQ3: Benefits of treatment							
Isoniazid vs placebo	Main analysis: 1 RCT (27 830)[a] Sensitivity analysis: 5 RCTs (36 823)	Developing active tuberculosis Main analysis: RR, 0.35 at 5 y of follow-up (95% CI, 0.24-0.52) for 24 weeks[b] of isoniazid vs placebo; NNT = 112 Sensitivity analysis: pooled RR, 0.31 at 2 to 10 y of follow-up[c] (95% CI, 0.24-0.41) Deaths due to tuberculosis 0 vs 3 deaths; RR, 0.14 (95% CI, 0.01-2.78) for combined isoniazid groups vs placebo	Consistency NA for the single study; reasonably precise for developing active tuberculosis but imprecise for other outcomes Consistent across RCTs used in sensitivity analysis (I^2 = 0%); precise	Good (fair to good for sensitivity analysis)	Studies used in sensitivity analysis used longer duration (1 y of isoniazid)[d] and some used doses lower or higher than currently recommended; 1 trial was poor quality Small number of events for deaths due to tuberculosis Reporting bias not detected	High for benefit of isoniazid vs placebo for reducing risk of developing active tuberculosis Low for benefit for reducing deaths due to tuberculosis Insufficient for all-cause mortality	Study population in main analysis trial included those with fibrotic pulmonary lesions and a ≥6-mm TST induration; median age 50 y; trials in main and sensitivity analysis published >40 y ago Trials in sensitivity analysis enrolled household contacts of active cases, veterans with inactive pulmonary tuberculosis, persons residing in mental institutions, and military members exposed to an active tuberculosis case
Rifampin vs isoniazid	2 RCTs (6910)	Developing active tuberculosis: 8 vs 9; 2 RCTs (6910) All-cause mortality: 22 vs 15; 2 RCTs (6910) Deaths due to tuberculosis: 0 vs 0; 1 RCT (847)	Consistency unknown, imprecise	Fair to good	Open-label Unclear allocation concealment No events for deaths due to tuberculosis	Low for noninferiority of shorter-duration rifampin Insufficient for deaths due to tuberculosis	Study population included those 18 y or older with a positive TST/IGRA result Second study required patients to be at increased risk of progression to active tuberculosis About half of participants were aged 18-35 y

(continued)

Table 2. Summary of Evidence on Screening for and Treatment of LTBI in Adults (continued)

Topic	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
Rifapentine + isoniazid vs isoniazid alone	2 RCTs (7149)[e]	Developing active tuberculosis: 5 vs 10;[f] 1 RCT (6886)[e] Deaths due to tuberculosis: 0 vs 0; 1 RCT (263) All-cause mortality: 30 vs 34; 2 RCTs (7149)	Consistency NA, single study for each outcome; reasonably precise for developing active tuberculosis and all-cause mortality, and imprecise for deaths due to tuberculosis	Fair	Both studies were open label; no data for deaths due to tuberculosis; differential noncompletion and withdrawal rates in 1 study	Low for noninferiority of rifapentine + isoniazid Insufficient for deaths due to tuberculosis Low for all-cause mortality for noninferiority of rifapentine + isoniazid	In the larger trial, median age 37 y; 57% White; combined intervention was directly observed therapy once weekly for 3 mo; high-risk participants; most had a close contact with an active tuberculosis case; 25% were included solely because of recent TST conversion In the smaller trial, mean age 32 y; all participants had close contact with an active tuberculosis case and had a positive TST result within 1 mo after exposure
KQ4: Harms of screening							
	0	No eligible studies	NA	NA	NA	Insufficient	NA
KQ5: Harms of treatment							
Isoniazid vs placebo	Main analysis: 1 RCT (27 830)[a] Sensitivity analysis for hepatotoxicity: 4 RCTs (35 161) Sensitivity analysis for discontinuation due to adverse events: 4 RCTs (55 398)	Hepatotoxicity at 5 y: RR, 4.59 (95% CI, 2.03-10.39) for isoniazid (24 wk) vs placebo; NNH = 279 Sensitivity analysis: pooled RR, 5.04 (95% CI, 2.50-10.15; I^2 = 0%) Dose-response effect seen with increased risk with longer treatment duration Death from hepatotoxicity: 0 in placebo group, 0.14 per 1000 receiving isoniazid; RR, 2.35 (95% CI, 0.12-45.46); NNH = 6947 Discontinuation of treatment due to adverse events: RR, 1.50 (95% CI, 1.18-1.89); NNH = 167 Sensitivity analysis: pooled RR, 1.58 (95% CI, 1.00-2.49) Gastrointestinal adverse events: RR, 1.33 (95% CI, 1.01-1.75) Sensitivity analysis: different outcomes reported across studies; no differences among groups	Consistency NA, single study in main analysis; consistent across studies in sensitivity analysis; imprecise for hepatotoxicity; reasonably precise for discontinuation due to adverse events and other gastrointestinal adverse events	Fair	Harm ascertainment techniques not well described Studies used in sensitivity analysis limited by ascertainment bias Small number of events for some outcomes	Moderate for harm for hepatotoxicity and discontinuation due to adverse events Low for harm for other gastrointestinal adverse events	Study population in main analysis trial includes those with fibrotic pulmonary lesions and a ≥6-mm TST induration; median age 50 y; trials completed >40 y ago Trials in sensitivity analysis enrolled employees in a US hospital, individuals meeting ATS criteria referred to a US military medical center, and veterans with inactive pulmonary tuberculosis
Isoniazid vs rifampin	4 RCTs (7390)	Hepatotoxicity: pooled RR, 4.22 (95% CI, 2.21-8.06); 3 trials (7339) Death from hepatotoxicity: no events reported in any groups of any study Discontinuations due to adverse events: RR, 2.25 (95% CI, 0.90-5.59); 3 trials (7339) Gastrointestinal intolerance: total of 20 vs 19 events across trials; calculated RRs for the 2 trials with sufficient data were 0.34 (95% CI, 0.03-3.23) and 1.16 (95% CI, 0.62-2.19)	Consistent; precise for hepatotoxicity Inconsistent; imprecise for discontinuation due to adverse events and gastrointestinal intolerance	Fair to good	3 trials were open label, 1 trial with high attrition; duration of follow-up may be inadequate for some outcomes; for gastrointestinal intolerance, concern for ascertainment bias	High for greater risk of hepatotoxicity with isoniazid Low for discontinuations due to adverse events Insufficient for gastrointestinal intolerance	Trials published in 2004, 2008, 2012, 2018; participants had positive TST result following Canadian guidelines or were inmates diagnosed with LTBI at jail entry

(continued)

Table 2. Summary of Evidence on Screening for and Treatment of LTBI in Adults (continued)

Topic	No. of studies (No. of participants)	Summary of findings	Consistency and precision	Study quality	Limitations (including reporting bias)	Overall strength of evidence	Applicability
Rifapentine + isoniazid vs isoniazid alone	2 RCTs (7149)[e]	Hepatotoxicity PREVENT TB trial: Grade 3 or 4: 210 vs 219; RR, 0.90 (95% CI, 0.75-1.08) Attributable to study drug: 17 vs 97; RR, 0.16 (95% CI, 0.10-0.28) Sun et al[123]: AST/ALT >3× 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 Discontinuation due to adverse event PREVENT TB trial: 186 vs 136; RR, 1.28 (95% CI, 1.03-1.59) Sun et al[123]: 12 vs 7; RR, 1.70 (95% CI, 0.69-4.19) Systemic drug reactions and hypersensitivity PREVENT TB trial: Possible hypersensitivity: 146 vs 17; RR, 8.04 (95% CI, 4.88-13.26) Any clinically significant systemic drug reaction: 138 vs 15; RR, 8.7 (95% CI 5.1-14.7) Sun et al[123]: 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 study had high overall attrition, and the other had higher withdrawal and noncompletion rates in 1 group	Low favoring less hepatotoxicity with rifapentine + isoniazid Moderate favoring lower discontinuation due to adverse event with isoniazid Low favoring fewer systemic drug reactions with isoniazid	PREVENT TB trial published in 2011, data were from the HIV-negative subgroup with TST or IGRA confirmation; combined intervention was directly observed therapy once weekly for 3 mo; high-risk individuals; most had close contact with an active tuberculosis case; 25% were included solely because of recent TST conversion One study completed in Taiwan, all participants had close contact with an active tuberculosis case and had positive TST result within 1 mo after exposure

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATS, American Thoracic Society; IGRA, interferon-gamma release assay; KQ, key question; LTBI, latent tuberculosis infection; NA, not applicable; NNH, number needed to harm; PPD, purified protein derivative; QFT-GIT, QuantiFERON-TB Gold-In-Tube (3rd-generation test); QFT-Plus, QuantiFERON-TB Gold Plus (4th-generation test); RCT, randomized clinical trial; RR, relative risk; T-SPOT.*TB*, commercial ELISPOT assay; TST, tuberculin skin test; ULN, upper limit of normal.

[a] Of the 27 830 participants in the IUAT trial, the only trial meeting all eligibility criteria for KQ3 that compared isoniazid with placebo, 6965 were treated with a US Centers for Disease Control and Prevention (CDC)–approved regimen (isoniazid [300 mg for 24 weeks]). The IUAT trial randomized 27 830 participants to isoniazid (300 mg for 12 weeks [6956]), isoniazid (300 mg for 24 weeks [6965]), isoniazid (300 mg for 52 weeks [6919]), or placebo (6990).

[b] The relative risks for the other treatment groups developing active tuberculosis 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.

[c] Follow-up for the 5 RCTs included in the sensitivity analysis ranged from 2 to 10 years; 1 study followed up patients for 2 years, 1 for 5 years (IUAT), 2 for 7 years, and 1 for 10 years.

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

[e] One open-label, noninferiority trial randomized 7731 participants; data were obtained from the CDC on the subset of participants most directly relevant for this review: the 6886 adults (aged ≥18 years) who were HIV-negative and TST- or IGRA-positive.

[f] The combination therapy group was found to be noninferior to the isoniazid-only group.

(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 tuberculosis (which has decreased), treatments for active tuberculosis, or likelihood of LTBI progressing to active tuberculosis would significantly change estimates of effectiveness. Trials comparing isoniazid with placebo mostly evaluated long durations of treatment (eg, 1 year of isoniazid) that were recommended at the time.

Early studies of isoniazid indicated a 4- to 5-fold increase in hepatotoxicity compared with placebo, although deaths due to hepatotoxicity were very rare—a total of 3 participants in IUAT, all of whom had continued to take isoniazid after liver abnormalities were recognized. After the effectiveness of isoniazid was established, subsequent studies evaluated shorter durations of treatment and other regimens to focus on harm reduction, improving adherence, or both. 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, isoniazid plus rifapentine, and isoniazid plus rifampin) than with isoniazid alone.

Limitations

This review had several limitations. First, it did not cover testing of close contacts of persons with active tuberculosis (usually managed by public health programs) or high-risk populations for whom LTBI testing is considered part of standard disease management (eg, persons with HIV, persons with planned or active use of tumor necrosis factor inhibitors or other targeted immune modulators). Second, the applicability of the available studies was somewhat uncertain because of the populations enrolled or the trials being conducted more than 40 years ago. Third, no eligible studies focusing on pregnant women were found.

Conclusions

No studies evaluated the direct benefits and harms of screening for LTBI compared with no screening. TST and IGRAs were moderately sensitive and highly specific. Treatment of LTBI with recommended regimens reduced the risk of progression to active tuberculosis. Isoniazid was associated with higher rates of hepatotoxicity than placebo or rifampin.

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