

# Screening for Latent Tuberculosis Infection in Adults

## US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**IMPORTANCE** Tuberculosis remains an important preventable disease in the United States. An effective strategy for reducing the transmission, morbidity, and mortality of active disease is the identification and treatment of latent tuberculosis infection (LTBI) to prevent progression to active disease.

**OBJECTIVE** To issue a current US Preventive Services Task Force (USPSTF) recommendation on screening for LTBI.

**EVIDENCE REVIEW** The USPSTF reviewed the evidence on screening for LTBI in asymptomatic adults seen in primary care, including evidence dating from the inception of searched databases.

**FINDINGS** The USPSTF found adequate evidence that accurate screening tests for LTBI are available, treatment of LTBI provides a moderate health benefit in preventing progression to active disease, and the harms of screening and treatment are small. The USPSTF has moderate certainty that screening for LTBI in persons at increased risk for infection provides a moderate net benefit.

**CONCLUSIONS AND RECOMMENDATION** The USPSTF recommends screening for LTBI in populations at increased risk. (B recommendation)

JAMA. 2016;316(9):962-969. doi:10.1001/jama.2016.11046

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**Author/Group Information:** The USPSTF members are listed at the end of this article.

**Corresponding Author:** Kirsten Bibbins-Domingo, PhD, MD, MAS ([chair@uspstf.net](mailto:chair@uspstf.net))

**T**he US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

### Summary of Recommendation and Evidence

The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations at increased risk (B recommendation) (**Figure 1**).

### Rationale

#### Importance

In the United States, tuberculosis remains an important preventable disease, including active tuberculosis infection, which may be infec-

tious, and latent infection (LTBI), which is asymptomatic and not infectious but can later reactivate and progress to active disease. The precise prevalence rate of LTBI in the United States is difficult to determine; however, based on 2011-2012 National Health and Nutrition Examination Survey data, estimated prevalence is 4.7% to 5.0%.<sup>1</sup> Tuberculosis is spread through respiratory transmission. Approximately 30% of persons exposed to *Mycobacterium tuberculosis* will develop LTBI and, if untreated, approximately 5% to 10% of these persons will progress to active tuberculosis disease or reactivation of tuberculosis.<sup>2-6</sup> Rates of progression may be higher in persons with certain risk factors or medical conditions. An effective strategy for reducing the transmission, morbidity, and mortality of active tuberculosis disease is the identification and treatment of LTBI to prevent its progression to active disease. Traditionally, prevention of tuberculosis has relied on public health systems; however, more recently, screening for LTBI has become a relevant primary care issue.

#### Detection

The USPSTF found adequate evidence that accurate screening tests are available to detect LTBI. Screening tests include the Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs); both are moderately sensitive and highly specific.

#### Benefits of Early Detection and Treatment

The USPSTF found no studies that evaluated the direct benefits of screening for LTBI. The USPSTF found adequate evidence that treat-

Figure 1. US Preventive Services Task Force Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice		
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit	
Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

ment of LTBI with regimens recommended by the Centers for Disease Control and Prevention (CDC) decreases progression to active tuberculosis; the magnitude of this benefit is moderate.

**Harms of Early Detection and Treatment**

The USPSTF found no direct evidence on the harms of screening for LTBI. The USPSTF found adequate evidence that the magnitude of harms of treatment of LTBI with CDC-recommended regimens is small. The primary harm of treatment is hepatotoxicity.

**USPSTF Assessment**

The USPSTF concludes with moderate certainty that the net benefit of screening for LTBI in persons at increased risk for tuberculosis is moderate.

**Clinical Considerations**

**Patient Population Under Consideration**

This recommendation applies to asymptomatic adults 18 years and older at increased risk for tuberculosis (see the “Assessment of Risk” section for more information). It does not apply to adults with symptoms of tuberculosis or to children and adolescents (Figure 2).

**Assessment of Risk**

Populations at increased risk for LTBI based on increased prevalence of active disease and increased risk of exposure include persons who were born in, or are former residents of, countries with increased tuberculosis prevalence and persons who live in, or have

Figure 2. Screening for Latent Tuberculosis Infection in Adults: Clinical Summary

Population	Asymptomatic adults at increased risk for infection
Recommendation	Screen for latent tuberculosis infection (LTBI). Grade: B
Risk Assessment	Populations at increased risk for LTBI include persons who were born in, or are former residents of, countries with increased tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings (eg, homeless shelters and correctional facilities). Local demographic patterns may vary across the United States; clinicians can consult their local or state health departments for more information about populations at risk in their community.
Screening Tests	Screening tests include the Mantoux tuberculin skin test and interferon-gamma release assays; both are moderately sensitive and highly specific for the detection of LTBI.
Treatment and Interventions	The CDC provides recommendations for the treatment of LTBI at <a href="http://www.cdc.gov/tb/topic/treatment/ltni.htm">http://www.cdc.gov/tb/topic/treatment/ltni.htm</a> .
Balance of Benefits and Harms	The USPSTF concludes with moderate certainty that the net benefit of screening for LTBI in persons who are at increased risk for tuberculosis is moderate.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to <http://www.uspreventiveservicestaskforce.org>.



CDC indicates Centers for Disease Control and Prevention; USPSTF, US Preventive Services Task Force.

lived in, high-risk congregate settings (eg, homeless shelters and correctional facilities). Clinicians can consult their local or state health departments for more information about populations at risk in their community, because local demographic patterns may vary across the United States.

In 2015, among persons of known national origin, 66.2% of all active tuberculosis cases in the United States were among foreign-born persons, and the case rate of active tuberculosis among foreign-born persons was approximately 13 times higher than among US-born persons (15.1 vs 1.2 cases per 100 000 persons).<sup>7</sup> More than half of all foreign-born persons in the United States with active tuberculosis were from 5 countries: Mexico, the Philippines, Vietnam, India, and China.<sup>7</sup> In addition, the CDC has identified foreign-born persons from Haiti and Guatemala as important contributors to active tuberculosis cases in the United States.<sup>8</sup> The World Health Organization (WHO) recently updated its list of countries with a high burden of tuberculosis to include the top 20 countries with the highest absolute numbers of cases and an additional 10 countries with the most severe burden in terms of case rate per capita.<sup>9</sup>

Persons who live in, or have lived in, high-risk congregate settings also have a higher prevalence rate of active tuberculosis and increased risk for exposure. Among persons 15 years and older with active tuberculosis, 5.6% were homeless within the past year, 2.2% were residents of a long-term care facility, and 4.2% were in a correctional facility at the time of diagnosis.<sup>10</sup> Published prevalence rates of LTBI in these settings vary widely, depending on the type of screening test used, the TST threshold used to define the presence of LTBI, and the population studied. Estimates of LTBI prevalence range from 23.1% to 87.6% among

prisoners and from 18.6% to 79.8% among persons who are homeless.<sup>2,11</sup>

Other populations at increased risk for LTBI or progression to active disease include persons who are immunosuppressed (eg, persons living with human immunodeficiency virus [HIV], patients receiving immunosuppressive medications such as chemotherapy or tumor necrosis factor- $\alpha$  inhibitors, and patients who have received an organ transplant) and patients with silicosis (a lung disease). However, given that screening in these populations may be considered standard care as part of disease management or indicated prior to the use of certain medications, the USPSTF did not review evidence on screening in these populations. Some evidence from observational studies has explored the association between poorly controlled diabetes and progression of LTBI to active disease. However, there is insufficient evidence on screening for and treatment of LTBI in persons with diabetes for the USPSTF to make a separate recommendation for this important subgroup.

Persons who are contacts of individuals with active tuberculosis, health care workers, and workers in high-risk congregate settings may also be at increased risk of exposure. Because screening in these populations is conducted as part of public health<sup>12</sup> or employee health<sup>13,14</sup> surveillance, the USPSTF did not review the evidence in these populations. Clinicians seeking further information about testing for tuberculosis in these populations can refer to the "Useful Resources" and "Recommendations of Others" sections.

**Screening Tests**

Two types of screening tests for LTBI are currently available in the United States: the TST and IGRA. The TST requires intradermal placement of purified protein derivative and interpretation of response

48 to 72 hours later. The skin test reaction is measured in millimeters of the induration (a palpable, raised, hardened area or swelling). Interferon-gamma release assays require a single venous blood sample and laboratory processing within 8 to 30 hours after collection. Two types of IGRAs are currently approved by the US Food and Drug Administration: T-SPOT.TB (Oxford Immunotec Global) and QuantiFERON-TB Gold In-Tube (Qiagen).

Numerous patient and systems factors may influence the selection of a screening test.<sup>15</sup> Generally, the CDC recommends screening with either the TST or IGRA but not both. Testing with IGRAs may be preferable for persons who have received a BCG vaccination or persons who may be unlikely to return for TST interpretation. Additional information on the use and interpretation of the TST and IGRA is available from the CDC.<sup>16</sup>

### Screening Intervals

The USPSTF found no evidence on the optimal frequency of screening for LTBI. Depending on specific risk factors, screening frequency could range from 1-time only screening among persons who are at low risk for future tuberculosis exposure to annual screening among those who are at continued risk of exposure.

### Treatment

Recommendations for the treatment of LTBI are available from the CDC.<sup>17</sup>

## Additional Approaches to Prevention

The public health system has an essential role in the control and elimination of tuberculosis. Clinicians are required to report cases of active tuberculosis to their local health department. As outlined by local and state public health laws, local health departments investigate and ensure treatment of active tuberculosis cases and perform contact tracing and medical surveillance of contacts.

Occupational health services also have an important role in the prevention and control of tuberculosis. Certain work settings (health care settings, correctional facilities, and other high-risk congregate housing settings) may pose a higher risk of tuberculosis exposure, and employers often have an important role in preventing tuberculosis exposure among employees and performing medical surveillance of employees for exposure.

### Useful Resources

Clinicians seeking guidance on tuberculosis management among persons living with HIV can obtain additional information from the National Institutes of Health.<sup>18</sup> Clinicians seeking information on medical surveillance of contacts of persons with active tuberculosis can contact their local health department, review their local public health law, or review guidance from the CDC.<sup>19</sup> The CDC also provides information for public health tuberculosis programs.<sup>20</sup>

Clinicians seeking information on medical surveillance of health care workers or employees working in high-risk settings can consult resources from the CDC and the Occupational Safety and Health Administration.<sup>21-23</sup> Clinicians seeking guidance on screening for LTBI in children can find more information on the American Academy of Pediatrics' Bright Futures website.<sup>24</sup> Clinicians seeking guidance on tuberculosis and pregnancy can obtain information from the CDC.<sup>25</sup>

## Other Considerations

### Implementation

Screening with the TST requires that patients return 48 to 72 hours after administration of the skin test for interpretation of results. When placing a TST, clinicians should plan with patients accordingly to ensure they can return in time and that the facility is able to interpret the test results within the proper time frame.<sup>26</sup> Screening with an IGRA requires obtaining a single venous blood sample, and patients do not need to return for interpretation of results. However, clinicians should be aware of processing requirements for blood samples and ensure that venous blood samples are drawn and can reach the laboratory for processing within the appropriate time frame (8-30 hours, depending on the test).<sup>27</sup>

### Research Needs and Gaps

Further research is needed that evaluates risk assessment tools to determine efficient ways of identifying candidates for LTBI testing and treatment. Additional research on how often LTBI screening should be performed in different subpopulations is also needed. The USPSTF identified no studies on LTBI screening or treatment in pregnant women and the potential effects on the fetus; this represents an important gap in the literature that needs further research. In addition, more studies are needed to clarify whether certain screening methods are preferable for certain risk groups.

## Discussion

### Burden of Disease

Tuberculosis causes a substantial health burden globally. Approximately one-third of the world's population is infected with tuberculosis; in 2014, 9.6 million persons were estimated to have contracted tuberculosis, and an estimated 1.5 million deaths related to tuberculosis infection occurred worldwide.<sup>9</sup> In the United States, 9563 new active cases of tuberculosis were reported in 2015, which corresponds to an incidence rate of 3.0 cases per 100 000 persons.<sup>7</sup> In 2013, 555 deaths from tuberculosis were reported in the United States.<sup>28</sup> In 2015, half of all tuberculosis cases occurred in 4 states: California, Texas, New York, and Florida. Asians represented the largest percentage of total cases (33%), followed by Hispanics (28%), African Americans (21%), and whites (13%); American Indian or Alaska Natives and Native Hawaiian or other Pacific Islanders each represented approximately 1% of cases.<sup>7</sup> Incidence rates of active tuberculosis may be higher in populations at increased risk, owing to greater likelihood of exposure (eg, persons who have lived in countries with a high tuberculosis burden) or greater likelihood of progression from LTBI to active disease (eg, persons who are immunosuppressed). Although LTBI is asymptomatic, signs and symptoms of active tuberculosis disease may include cough, hemoptysis (coughing up blood), unexplained weight loss, night sweats, fevers, chills, and fatigue.

### Scope of Review

The USPSTF commissioned a systematic review of the evidence on screening for LTBI.<sup>2,3</sup> Evidence dating from the inception of searched databases until August 3, 2015, was included. The review focused

on evidence about screening for LTBI in asymptomatic adults seen in primary care settings. It did not include evidence on screening in persons for whom LTBI screening would be considered management of a specific condition (eg, persons living with HIV), public health surveillance (ie, tracing contacts of persons with active tuberculosis disease), surveillance of employees working in high-risk settings, or screening indicated prior to the use of specific immunosuppressive medications.

### Accuracy of Screening Tests

There is no direct test for the diagnosis of latent infection with *M tuberculosis*. Following screening, diagnosis of LTBI is based on medical history, physical examination, and exclusion of active tuberculosis disease. In the absence of a reference standard for detection of LTBI, screening test performance is based on detection of disease in persons with known active tuberculosis and nondetection of disease in populations at low risk for the disease and presumed not to have LTBI or active tuberculosis.

The USPSTF identified 67 good- or fair-quality studies that provided information on the accuracy and reliability of screening tests for LTBI.<sup>2</sup> For studies reporting on sensitivity, 8 were conducted in countries with a high burden of tuberculosis, 29 were conducted in countries with an intermediate burden, 10 were conducted in countries with a low burden, and 3 were conducted in countries with a mix of low to intermediate burden. For studies reporting on specificity, 3 were conducted in countries with an intermediate burden; 14 were conducted in countries with a low burden; and 1 was conducted in 2 countries: 1 with an intermediate burden and 1 with a low burden.

When using a positive threshold of 10 mm of induration, the TST has moderate sensitivity and high specificity for detection of LTBI. Based on pooled analyses of studies reviewed by the USPSTF, when using a positive threshold of 10 mm, the TST has sensitivity of 79% (11 studies;  $n = 988$ ) and specificity of 97% (9 studies;  $n = 9651$ ).<sup>2</sup>

Pooled analyses of the T-SPOT.TB test (a type of IGRA) indicate sensitivity of 90% (16 studies;  $n = 984$ ) and specificity of 95% (5 studies;  $n = 1810$ ). Pooled analyses of the QuantiFERON-TB Gold In-Tube test (another type of IGRA) indicate sensitivity of 80% (24 studies;  $n = 2321$ ) and specificity of 97% (4 studies;  $n = 2053$ ). The USPSTF identified no studies that evaluated the accuracy and reliability of sequential screening strategies.

### Effectiveness of Early Detection and Treatment

The USPSTF identified no randomized clinical trials that compared screening with no screening to provide direct evidence of the benefit of screening for LTBI on health outcomes, such as rates of active tuberculosis disease, disease-specific or all-cause mortality, or tuberculosis transmission. Three good- or fair-quality trials ( $n = 35\,563$ ) conducted in Canada, Brazil, Saudi Arabia, Spain, Czechoslovakia, Finland, Germany, Hungary, Poland, Romania, and Yugoslavia provided evidence on the benefits of treatment of LTBI.<sup>2</sup> Trials evaluated treatment with isoniazid,<sup>29</sup> rifampin,<sup>30</sup> and rifapentine plus isoniazid.<sup>31</sup>

The best evidence on the effectiveness of treatment was from the International Union Against Tuberculosis (IUAT) trial. This good-quality randomized clinical trial was conducted in 7 European countries (Czechoslovakia, Finland, Germany, Hungary,

Poland, Romania, and Yugoslavia) among participants with fibrotic pulmonary lesions but not active tuberculosis. The trial, published in 1982, included 27 830 participants and evaluated treatment with daily isoniazid. It found that at 5 years, the relative risk (RR) of progression to active tuberculosis was 0.35 (95% CI, 0.24-0.52) for treatment with isoniazid (300 mg daily for 24 weeks) compared with placebo. The trial reported fewer deaths attributable to tuberculosis among participants receiving treatment with isoniazid (0 vs 3 deaths in the placebo group; RR, 0.14 [95% CI, 0.01-2.78]), although this difference was not statistically significant.

The other 2 treatment trials compared either rifampin with isoniazid and found zero deaths in either group or rifapentine plus isoniazid with isoniazid alone and found that the combination therapy was noninferior in preventing progression to active tuberculosis. None of the treatment studies reported on transmission rates of tuberculosis.

### Potential Harms of Screening and Treatment

The USPSTF identified no studies that directly reported on the harms of screening. Potential harms include stigma associated with screening and diagnostic workup and treatment of false-positive results. Five good- or fair-quality studies ( $n = 36\,043$ ) conducted in the United States, Canada, Saudi Arabia, Brazil, Spain, Czechoslovakia, Finland, Germany, Hungary, Poland, Romania, and Yugoslavia reported on the harms of treatment.<sup>2,29-33</sup> Interventions evaluated included isoniazid, rifampin, and rifapentine plus isoniazid. The most consistently reported harm was hepatotoxicity. The only study that assessed harms of treatment vs placebo was the IUAT trial,<sup>30</sup> which found an RR of 4.59 (95% CI, 2.03-10.39) for hepatotoxicity at 5 years among participants being treated with isoniazid (300 mg for 24 weeks) vs placebo. The IUAT trial also reported more deaths from hepatotoxicity among participants being treated with isoniazid than with placebo, although this finding was not statistically significant (0.14 vs 0 deaths per 1000 persons; RR calculated from published data, 2.35 [95% CI, 0.12-45.46]).

The other trials compared either rifampin<sup>30,32,33</sup> or rifapentine plus isoniazid<sup>31</sup> with isoniazid. Meta-analysis of 3 trials of rifampin compared with isoniazid found a higher RR for hepatotoxicity among participants being treated with isoniazid (RR, 3.29 [95% CI, 1.72-6.28]).<sup>2</sup> None of these trials, which were more recent than the IUAT trial, reported any deaths from hepatotoxicity. The 1 study that reported on hepatotoxicity of rifapentine plus isoniazid vs isoniazid alone found a nonsignificant reduced RR of 0.90 (95% CI, 0.75-1.08) for grade 3 or 4 hepatotoxicity among participants being treated with rifapentine plus isoniazid. There also was a nonsignificant reduced RR of death from hepatotoxicity among participants being treated with rifapentine plus isoniazid vs isoniazid alone (RR, 0.83 [95% CI, 0.51-1.35]).

A few studies also reported on gastrointestinal adverse events. Compared with placebo, participants treated with isoniazid had a higher risk of medication discontinuation because of gastrointestinal adverse events (RR, 1.33 [95% CI, 1.01-1.75]).<sup>29</sup> Compared with rifampin, treatment with isoniazid had a nonsignificant increased RR of gastrointestinal adverse events (RR, 1.60 [95% CI, 0.76-3.40]) in 2 studies.<sup>2</sup> All 5 studies also reported on discontinuation of treatment because of adverse events. Compared with placebo, treatment with isoniazid had an RR of medi-



cation discontinuation of 1.50 (95% CI, 1.18-1.89).<sup>29</sup> Pooling results from the 3 studies of isoniazid vs rifampin found a nonsignificant increased risk of discontinuation with isoniazid (RR, 1.61 [95% CI, 0.57-4.57]).<sup>2</sup> The study of rifapentine plus isoniazid vs isoniazid alone found an increased risk of discontinuation with rifapentine plus isoniazid (RR, 1.28 [95% CI, 1.03-1.59]).<sup>31</sup>

### Estimate of Magnitude of Net Benefit

Overall, the USPSTF found adequate evidence that accurate screening tests for LTBI are available, treatment of LTBI provides a moderate health benefit in preventing progression to active disease, and the harms of screening and treatment are small. The USPSTF has moderate certainty that screening for LTBI in persons at increased risk for infection provides a moderate net benefit. The USPSTF estimated that if a hypothetical cohort of 100 000 asymptomatic adults at increased risk for tuberculosis (eg, persons born in, or former residents of, high-prevalence countries) were screened, 52 to 146 active tuberculosis cases would be prevented, 7 to 67 cases of hepatotoxicity would occur (depending on type of treatment), and 111 persons would discontinue treatment because of adverse events. The number needed to treat to prevent 1 case of LTBI from progressing to active tuberculosis would range from 111 to 314 (depending on the patient's risk for progression), and the number needed to harm to cause 1 case of hepatotoxicity from treatment would range from 279 to 2531 (depending on type of treatment). These estimates are based on prevalence data from the 2011-2012 National Health and Nutrition Examination Survey<sup>1</sup> and numerous assumptions about screening sensitivity and specificity (eg, using the TST with a 10-mm threshold for a positive diagnosis) and potential benefits of treatment (eg, estimated efficacy of treatment for 24 weeks of isoniazid, based on IUAT trial findings). Further information on the assumptions used is available in the corresponding evidence review.<sup>2</sup>

### How Does Evidence Fit With Biological Understanding?

Tuberculosis disease is caused by *M tuberculosis*, which is spread through airborne transmission when a person with active pulmonary tuberculosis coughs or sneezes. When the tuberculosis bacillus is inhaled, a person can either clear *M tuberculosis*; develop active disease (primary tuberculosis disease), which may be infectious; or develop latent infection (LTBI), which is asymptomatic and not infectious. Latent infection can later reactivate and progress to active tuberculosis disease. Approximately 30% of persons exposed to active *M tuberculosis* will develop LTBI.<sup>2</sup> Approximately 5% to 10% of persons with a positive TST result will experience reactivation of LTBI and progress to active tuberculosis disease.<sup>2-6</sup>

### Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from March 8 to April 4, 2016. Many comments sought clarification around risk assessment of populations who should receive screening. The USPSTF clarified that given regional variations in the local populations considered at risk for tuberculosis, clinicians may consult their local or state public health agency for additional details on specific populations at risk in their community. Furthermore, the USPSTF clarified that although persons with diabetes and pregnant women are not addressed separately in this recommendation statement, they are also not

excluded from the recommendation. A few public comments sought clarification on the recommended frequency of screening. Although the USPSTF sought evidence on screening frequency, there was not enough evidence available to determine an optimal screening interval. Several comments requested that the recommendation include treatment of LTBI. While the USPSTF acknowledges that treatment of LTBI contributes to the success of LTBI screening, it is beyond the scope of the USPSTF to make any specific recommendations on treatment. The CDC provides treatment guidelines for LTBI.<sup>17</sup>

## Update of Previous USPSTF Recommendation

The USPSTF last issued a recommendation on screening for tuberculosis in 1996. At that time, the USPSTF recommended screening for tuberculosis infection with the TST in asymptomatic, high-risk persons (A recommendation) and consideration of BCG vaccination for selected high-risk individuals only (B recommendation). Given the changes in the epidemiology of the disease, the development of newer screening technologies, and newer methods for developing evidence-based recommendations, the USPSTF decided to update the topic and issue a recommendation using its current methodology and considering all of the available evidence, including studies published prior to 1996.

## Recommendations of Others

The American Academy of Family Physicians recommends screening for LTBI in populations at increased risk.<sup>34</sup> In 2005, the CDC, the American Thoracic Society, and the Infectious Diseases Society of America issued joint guidelines recommending that clinicians screen for LTBI only among high-risk populations and when treatment is feasible.<sup>35</sup> In its 2013 "Guide for Primary Health Care Providers," the CDC recommended targeted testing for tuberculosis among high-risk populations only.<sup>8</sup> The CDC identifies persons at risk for developing tuberculosis as those who have an increased likelihood of exposure to persons with tuberculosis disease (known close contacts of a person with infectious tuberculosis disease, persons who have immigrated from tuberculosis-endemic regions of the world, and persons who work or reside in facilities or institutions with those at high risk for tuberculosis) or persons with clinical conditions or other factors associated with an increased risk of progression from LTBI to tuberculosis disease (HIV infection, injection drug use, radiographic evidence of prior healed tuberculosis, low body weight, or other medical conditions). Further information on targeted testing is available from the CDC.<sup>36</sup>

The WHO also recently issued guidelines on the management of LTBI. For high-income countries with an estimated tuberculosis incidence of less than 100 cases per 100 000 persons (such as the United States), the WHO recommends systematic testing for and treatment of LTBI among persons living with HIV, adult and child contacts of persons with pulmonary tuberculosis, patients initiating anti-tumor necrosis factor treatment, patients receiving dialysis, patients preparing for an organ or hematologic transplant, and patients with silicosis. Either an IGRA or the TST should be used. The WHO also recommends considering

systematic testing and treatment among prisoners, health care workers, immigrants from high-burden countries, homeless persons, and illicit drug users. Either an IGRA or the TST should be used. It does not recommend systematic testing for LTBI among

persons who have diabetes, engage in harmful alcohol use, smoke tobacco, or are underweight, unless they are already included in the above recommendations.<sup>37</sup> Further information is available from the WHO.<sup>38</sup>

## ARTICLE INFORMATION

### Authors/US Preventive Services Task Force

**(USPSTF) members:** Kirsten Bibbins-Domingo, PhD, MD, MAS; David C. Grossman, MD, MPH; Susan J. Curry, PhD; Linda Bauman, PhD, RN, APRN; Karina W. Davidson, PhD, MASc; John W. Epling Jr, MD, MEd; Francisco A.R. García, MD, MPH; Jessica Herzstein, MD, MPH; Alex R. Kemper, MD, MPH, MS; Alex H. Krist, MD, MPH; Ann E. Kurth, PhD, RN, MSN, MPH; C. Seth Landefeld, MD; Carol M. Mangione, MD, MSPH; William R. Phillips, MD, MPH; Maureen G. Phipps, MD, MPH; Michael P. Pignone, MD, MPH.

### Affiliations of Authors/US Preventive Services Task Force (USPSTF) members:

University of California, San Francisco (Bibbins-Domingo); Group Health Research Institute, Seattle, Washington (Grossman); University of Iowa, Iowa City (Curry); University of Wisconsin-Madison (Bauman); Columbia University, New York, New York (Davidson); State University of New York Upstate Medical University, Syracuse (Epling); Pima County Department of Health, Tucson, Arizona (García); Independent consultant, Washington, DC (Herzstein); Duke University, Durham, North Carolina (Kemper); Fairfax Family Practice Residency, Fairfax, Virginia (Krist); Virginia Commonwealth University, Richmond (Krist); Yale University, New Haven, Connecticut (Kurth); University of Alabama at Birmingham (Landefeld); University of California, Los Angeles (Mangione); University of Washington, Seattle (Phillips); Brown University, Providence, Rhode Island (Phipps); University of Texas at Austin (Pignone).

**Author Contributions:** Dr Bibbins-Domingo 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. The USPSTF members contributed equally to the recommendation statement.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported. Authors followed the policy regarding conflicts of interest described at <http://www.uspreventiveservicestaskforce.org/Page/Name/conflict-of-interest-disclosures>. All members of the USPSTF receive travel reimbursement and an honorarium for participating in USPSTF meetings.

**Funding/Support:** The USPSTF is an independent, voluntary body. The US Congress mandates that the Agency for Healthcare Research and Quality (AHRQ) support the operations of the USPSTF.

**Role of the Funder/Sponsor:** AHRQ staff assisted in the following: development and review of the research plan, commission of the systematic evidence review from an Evidence-based Practice Center, coordination of expert review and public comment of the draft evidence report and draft recommendation statement, and the writing and preparation of the final recommendation statement and its submission for publication. AHRQ staff had

no role in the approval of the final recommendation statement or the decision to submit for publication.

**Disclaimer:** Recommendations made by the USPSTF are independent of the US government. They should not be construed as an official position of AHRQ or the US Department of Health and Human Services.

**Additional Contributions:** We thank Tina Fan, MD, MPH (AHRQ), who contributed to the writing of the manuscript, and Lisa Nicoletta, MA (AHRQ), who assisted with coordination and editing.

## REFERENCES

- Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. *PLoS One*. 2015;10(11):e0140881.
- Kahwati LC, Feltner C, Halpern M, et al. *Screening for Latent Tuberculosis Infection in Adults: An Evidence Review for the US Preventive Services Task Force: Evidence Synthesis No. 142*. Rockville, MD: Agency for Healthcare Research and Quality; 2016. AHRQ publication 14-05212-EF-1.
- Kahwati LC, Feltner C, Halpern M, et al. Primary care screening and treatment for latent tuberculosis infection in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2016.10357.
- Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc*. 1975;50(1):90-106.
- Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, Nguyen CH. Outcomes of contact investigations of infectious tuberculosis patients. *Am J Respir Crit Care Med*. 2000;162(6):2033-2038.
- American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161(4, pt 2):S221-S247.
- Salinas JL, Mindra G, Haddad MB, Pratt R, Price SF, Langer AJ. Leveling of tuberculosis incidence—United States, 2013-2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(11):273-278.
- Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. <http://www.cdc.gov/tb/publications/ltbi/>. 2014. Accessed July 7, 2016.
- World Health Organization. *Global Tuberculosis Report 2015*. 20th ed. Geneva, Switzerland: World Health Organization. [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/). 2015. Accessed July 21, 2016.
- Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2014. <http://www.cdc.gov/tb/statistics/reports/2014/default.htm>. 2014. Accessed July 7, 2016.
- Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med*. 2015;372(22):2127-2135.
- National Tuberculosis Controllers Association; Centers for Disease Control and Prevention (CDC). Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *MMWR Recomm Rep*. 2005;54(RR-15):1-47.
- Jensen PA, Lambert LA, Iademarco MF, Ridzon R; Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR Recomm Rep*. 2005;54(RR-17):1-141.
- Occupational Safety and Health Administration. *Enforcement Procedures and Scheduling for Occupational Exposure to Tuberculosis*. Washington, DC: Occupational Safety and Health Administration; 2015. Directive CPL O2-O2-078.
- Collins LF, Geadas C, Ellner JJ. Diagnosis of latent tuberculosis infection: too soon to pull the plug on the tuberculin skin test. *Ann Intern Med*. 2016;164(2):122-124.
- Centers for Disease Control and Prevention. Testing for tuberculosis (TB). [http://www.cdc.gov/tb/publications/factsheets/testing/tb\\_testing.htm](http://www.cdc.gov/tb/publications/factsheets/testing/tb_testing.htm). 2014. Accessed July 21, 2016.
- Centers for Disease Control and Prevention. Treatment regimens for latent TB infection (LTBI). <http://www.cdc.gov/tb/topic/treatment/ltbi.htm>. 2016. Accessed July 21, 2016.
- National Institutes of Health. AIDSinfo: guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb>. 2016. Accessed July 21, 2016.
- Centers for Disease Control and Prevention. TB guidelines. [http://www.cdc.gov/tb/publications/guidelines/list\\_date.htm](http://www.cdc.gov/tb/publications/guidelines/list_date.htm). 2012. Accessed July 21, 2016.
- Centers for Disease Control and Prevention. Resources for TB programs. <http://www.cdc.gov/tb/programs/default.htm>. 2014. Accessed July 21, 2016.
- Centers for Disease Control and Prevention. Infection control in health care settings. <http://www.cdc.gov/tb/topic/infectioncontrol/default.htm>. 2016. Accessed July 21, 2016.
- Centers for Disease Control and Prevention. TB in correctional facilities in the United States. <http://www.cdc.gov/tb/topic/populations/correctional/default.htm>. 2015. Accessed July 21, 2016.
- Occupational Safety and Health Administration, US Department of Labor. Tuberculosis: OSHA standards. <https://www.osha.gov/SLTC/tuberculosis/standards.html>. Accessed July 21, 2016.
- American Academy of Pediatrics. Bright Futures website. <https://brightfutures.aap.org/Pages/default.aspx>. 2016. Accessed July 21, 2016.

25. Centers for Disease Control and Prevention. TB and pregnancy. <http://www.cdc.gov/tb/topic/populations/pregnancy/default.htm>. 2014. Accessed July 21, 2016.
26. Centers for Disease Control and Prevention. Fact Sheet: tuberculin skin testing. <http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm>. 2016. Accessed February 23, 2016.
27. Centers for Disease Control and Prevention. Fact Sheet: interferon-gamma release assays (IGRAs)—blood tests for TB infection. <http://www.cdc.gov/tb/publications/factsheets/testing/igra.htm>. 2015. Accessed February 23, 2016.
28. Centers for Disease Control and Prevention. Fact Sheet: trends in tuberculosis, 2014. <http://www.cdc.gov/tb/publications/factsheets/statistics/tbtrends.htm>. 2015. Accessed February 23, 2016.
29. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ*. 1982;60(4):555-564.
30. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2008;149(10):689-697.
31. Sterling TR, Villarino ME, Borisov AS, et al; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166.
32. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. *Am J Respir Crit Care Med*. 2004;170(4):445-449.
33. White MC, Tulskey JP, Lee JR, et al. Isoniazid vs. rifampin for latent tuberculosis infection in jail inmates: toxicity and adherence. *J Correct Health Care*. 2012;18(2):131-142.
34. American Academy of Family Physicians. Clinical Preventive Services Recommendations. <http://www.aafp.org/patient-care/browse/type.tag-clinical-preventive-services-recommendations.html>. Accessed August 3, 2016.
35. Taylor Z, Nolan CM, Blumberg HM; American Thoracic Society; Centers for Disease Control and Prevention; Infectious Diseases Society of America. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2005;54(RR-12):1-81.
36. Centers for Disease Control and Prevention. Targeted testing for tuberculosis. <http://www.cdc.gov/tb/publications/tbi/targetedtesting.htm>. 2013. Accessed July 21, 2016.
37. World Health Organization. *Guidelines on the Management of Latent Tuberculosis Infection*. Geneva, Switzerland: World Health Organization; 2015.
38. World Health Organization. Tuberculosis (TB). <http://www.who.int/tb/en/>. 2016. Accessed July 21, 2016.