

# The Challenge of Latent TB Infection

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**Tuberculosis (TB)** is an enormous global public health problem and has emerged as the leading cause of death linked to a single pathogen: deaths attributable to TB now exceed



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those attributable to human immunodeficiency virus (HIV) (1.5 million vs 1.2 million in 2014).<sup>1</sup> The World Health Organization estimates that there were 9.6 million new TB cases in 2014.<sup>1</sup> The large majority of cases occur in low- and middle-income countries, especially in sub-Saharan Africa and Asia. In the United States, 9563 cases of TB were reported in 2015, for a rate of 3 cases per 100 000.<sup>2</sup> The global TB epidemic affects the United States because about two-thirds of US TB cases occur among non-US-born persons; higher rates of TB are also found among US-born persons of color.<sup>2</sup> Tuberculosis remains an important public health problem in selected geographic areas.<sup>2</sup> In 2013, 555 deaths attributable to TB were reported in the United States, the most recent year for which these data are available.<sup>3</sup>

Clinically, TB has been dichotomized into active disease (patients who are generally symptomatic and may be infectious if pulmonary disease is present) and latent infection (asymptomatic, noninfectious, but at variable risk for progression to active TB disease). There is increasing recognition that latent TB infection (LTBI) likely includes diverse responses to infection with *Mycobacterium tuberculosis* and, consequently, heterogeneous clinical outcomes. This includes individuals whose immunologic response is insufficient and who progress to primary active disease; those who have subclinical disease; those who initially contain infection but later progress to active TB disease; those who maintain persistent, lifelong asymptomatic infection; and those who may effectively clear infection by generating especially effective immune responses.<sup>4</sup> Certain epidemiologic factors are associated with an increased risk of progression to active TB, including recent infection (eg, contacts of persons with active TB) and HIV coinfection (the greatest risk factor for progression to active TB disease), but otherwise there is a lack of understanding and tools to predict who will and who will not progress from LTBI to active TB. This poses a major challenge to TB control and efforts to target screening and therapy for LTBI and complicates efforts to implement guidelines on how best to screen patients for LTBI in the United States.

An estimated 12.4 million persons in the United States have LTBI, with non-US-born persons representing an increasingly larger proportion (73%) of this group.<sup>5</sup> The World Health Organization, the Centers for Disease Control and Prevention (CDC),

and professional societies such as the Infectious Diseases Society of America and the American Thoracic Society have recommended targeted testing and treatment of high-risk individuals with LTBI as part of control strategies and efforts at TB elimination for the United States.<sup>2,6-8</sup> As noted by the US Preventive Services Task Force (USPSTF) and others, treatment of LTBI can significantly reduce the risk of progression to active disease with the greatest benefit among high-risk individuals.<sup>6,8-10</sup> Globally, there is growing interest in the diagnosis and treatment of LTBI and efforts to expand such activities beyond high-income, low-burden countries.<sup>11,12</sup> In the United States, there is increasing recognition that screening and treatment of LTBI among high-risk individuals should be part of primary care activities, especially if progress is to be made in enhancing TB control efforts and pre-elimination (defined as <1 TB case per 100 000 per year) and the ultimate goal of TB elimination. Thus, the USPSTF Recommendation Statement on screening in primary care settings for LTBI in adults and the accompanying Evidence Report and systematic review that provides support for the USPSTF recommendations, both of which are published in this issue of *JAMA*, are well timed.<sup>9,10</sup>

The USPSTF recommends screening for LTBI in populations at increased risk and gives this a “B” recommendation (“offer or provide this service”). However, the highest-risk populations and thus those with the greatest benefit for targeted screening and treatment (persons living with HIV, close contacts of persons with active TB, and those being treated with immunosuppressive agents such as tumor necrosis factor alpha inhibitors) were excluded from the USPSTF review of evidence because “screening in these populations may be considered standard care as part of disease management or indicated prior to the use of certain medications...” Once these highest-risk groups are removed, which patients are high risk in the primary care setting, and how should clinicians implement the USPSTF recommendations?

The USPSTF recommendations and systematic review include the standard estimate that the lifetime risk of active TB after infection is 5% to 10%. Although the risk varies widely, the majority of immunocompetent persons with LTBI do not progress to active TB disease. The risk of progression to active TB among persons with LTBI seen in primary care settings is incompletely defined, because the currently available diagnostic tests (including the tuberculin skin test and the interferon-gamma release assays [IGRAs]) have a poor predictive value for TB disease progression.<sup>8</sup> The USPSTF indicates that “many comments” were received on their draft guidelines that “sought clarification around risk assessment of populations who should receive screening.” Namely, who is considered at “high risk” in primary care settings and should be

targeted for screening and treatment of LTBI if present. The USPSTF answer: “clinicians may consult their local or state public health agency for additional details on specific populations at risk in their community.”

While there are geographic differences in risk factors for LTBI, the USPSTF may not have been able to provide additional guidance on how best to define “high risk” because of the lack of tools to know who will progress from LTBI to active disease. Currently, it is not possible to provide personalized medicine for LTBI, owing to a lack of understanding of TB biology. A recent study by Zak et al<sup>13</sup> suggests that blood biomarkers (in this study, whole-blood gene expression data) may be useful to identify individuals at risk for progression to active TB disease in otherwise healthy patients who have latent infection. Our hypothesis is that “immunologic signatures” related to antigen-specific T-cell responses may provide the ability to develop new biomarkers that predict disease progression.

Further guidance for clinicians (eg, from the CDC and state and local health departments) is needed to implement these USPSTF recommendations in primary care settings. Given that the highest-risk groups (eg, persons living with HIV, contacts of persons with active TB, persons who will receive tumor necrosis factor alpha inhibitors) were not part of the USPSTF scope of review, the most frequently encountered high-risk group will include immigrants from countries with high TB burden, which may represent the best target for screening in primary care settings. Other individuals at increased risk may include homeless persons, illicit drug users, and those who are incarcerated or who work in a correctional facility or other high-risk congregate settings such as homeless shelters. Risk assessment tools that have been developed by the CDC and the California Department of Public Health may be of use to clinicians in implementing the USPSTF recommendations.<sup>14,15</sup> The USPSTF notes that in the accompanying systematic review<sup>9</sup> there were insufficient data to make a recommendation for or against screening among persons with diabetes. Worldwide, especially in countries with high TB burden, diabetes and smoking are important risk factors.<sup>1</sup>

Harm does occur when screening low-risk US populations. Targeted testing for LTBI is recommended by the CDC and others because even with highly specific diagnostic tests, testing of low- or very low-risk populations will result in many false-positive results.<sup>6,16</sup> However, in the United States, extensive testing for LTBI is misguided when it involves testing low-risk individuals because of outdated state laws (that require food handlers, teachers, or other low-risk groups to be tested) or federal recommendations<sup>17</sup> or Occupational Safety

and Health Administration mandates related to testing of health care workers that have not kept up with the changing epidemiology of TB. Unlike countries with high TB burden, the vast majority of US health care workers are not at increased risk for occupationally acquired TB infection. However, tens or hundreds of thousands of low-risk US health care workers are required to undergo yearly testing for LTBI. This results in high rates of false-positive test results, especially if IGRAs are used for serial testing of low-risk health care workers.<sup>18</sup> Additional harm can be the consequence of toxicity of the drugs used to treat LTBI; this makes screening and accurate identification of those at high or low risk especially compelling.

Poor completion rates (<50% for those who agree to initiate therapy) complicate the challenge of treating LTBI.<sup>19</sup> Patients treated for LTBI are asymptomatic, regimens are long (up to 9 months), and clinicians are not able to provide patients with a precise estimate of the risk of progressing to active TB.

The USPSTF focused on CDC-recommended treatment regimens for LTBI.<sup>6,20</sup> These include 9 months of self-administered isoniazid, 4 months of self-administered rifampin, or 12 doses of weekly isoniazid plus rifapentine delivered by directly observed therapy. Primary care settings rarely have the resources to provide directly observed therapy. A recent report indicated that completion rates of self-administered weekly isoniazid/rifapentine was not inferior to directly observed therapy for the treatment of LTBI.<sup>21</sup> This study is likely to facilitate changes in CDC treatment guidelines for this regimen, with wider use in the primary care setting.

The USPSTF recommendations on screening for TB provide a service by focusing discussions on how to expand efforts on targeted testing and treatment of LTBI among adults seen in primary care settings. There will be challenges with implementation of these recommendations because of the current inability to precisely define individuals at high risk for progression to active TB. The recommendations also highlight the need for new and better tools for control of TB, including LTBI. In the short run, implementation science (operational research) will be needed to help facilitate the best ways of implementing the USPSTF recommendations. In the long run and to overcome the challenge of LTBI, new tools are needed including new and better diagnostic tests, biomarkers that have a high predictive value for identifying which patients are at risk for progression to active disease, and shorter, more effective, and better-tolerated regimens for treatment of LTBI. Such advancements will not be made without substantial investments in TB research by funders, including foundations and, most importantly, the United States and other governments from high- and middle-income countries.

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