JAMA editorial highlights challenges of implementing new TB screening guidelines

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An editorial in the Sept. 6, 2016 issue of *JAMA* accompanies the publication of new US Preventive Services Task Force (USPSTF) screening recommendations for latent tuberculosis (TB) infection in primary care settings. The editorial, entitled "The Challenge of Latent TB Infection," points out the urgent need for TB-related research to identify new tools and diagnostics that will identify patients who are at high risk from progressing from latent TB infection to active TB disease.

The editorial is co-authored by Henry M. Blumberg, MD, professor of medicine (infectious diseases), epidemiology, and global health at Emory University School of Medicine and Rollins School of Public Health, and Joel D. Ernst, MD, Jeffrey Bergstein Professor of Medicine at New York University School of Medicine.

"The USPSTF recommendations are a positive step in discussing how best to expand efforts to test and treat LTBI among adults in primary care settings," says Blumberg. "However, as noted in our editorial, the scientific community and physicians lack the tools to really know who is at high risk for progression from latent TB infection to active TB." An estimated 12.4 million people in the United States have latent TB infection, with non-US-born people representing an increasingly larger proportion (73 percent) of this group.

The lack of knowledge and tools highlights the importance of ongoing research leading to the development of better diagnostic tests and biomarkers that can predict which patients are at risk for progression

from latent to active disease, as well as better-tolerated treatment regimens for latent TB infections, note the authors.

Researchers increasingly recognize that latent TB infection includes diverse responses to infection with *Mycobacterium tuberculosis* (the pathogen that causes TB) and thus variable outcomes. Although latent TB infection progresses to active TB disease in a fraction of infected people, the scientific and medical communities lack the TB biology knowledge and tools that will predict who will progress. The identification of diagnostic tests or biomarkers that predict progression to active TB disease would greatly enhance TB control efforts in the United States and globally and allow physicians and public health officials to focus efforts on treatment of latent TB infection of those at greatest risk of progression to active, transmissible and potentially fatal disease.

"Currently, it is not possible to provide personalized medicine for persons with latent TB infection, owing to a lack of understanding of TB biology and lack of necessary tools to predict who is at greatest risk to progress to active TB disease," the authors write.

Blumberg and Ernst are co-PIs for one of four national Tuberculosis Research Units (TBRUs) launched in 2015 and supported by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). Researchers in the Emory/NYU TBRU, known as TBRU ASTRa are working to eliminate TB through a comprehensive understanding of antigen-specific T cell responses and their relationship to distinct outcomes of TB infection. Their primary hypothesis is that latent TB infection is a spectrum of three main immune states: (1) past, but cleared infection; (2) stable infection with a low risk of progression to active disease; or (3) infection with a high risk of progression to active TB disease.

By developing blood biomarkers and "immunologic signatures" related to antigen-specific T-cell responses, the researchers hope to identify individuals with latent TB infection who are at greatest risk for progression to active disease, allowing development of prevention strategies to target those at highest risk in areas with high rates of infection (usually low- and middle-income countries), as well as high income countries such as the U.S., where factors such as recent infection and HIV co-infection are associated with an increased risk of progression to active TB.

The World Health Organization (WHO) estimates there were 9.6 million new active TB cases globally in 2014, mostly in low- and middle-income countries in sub-Saharan Africa and Asia. TB has emerged as the leading cause of death due to a single pathogen: deaths attributable to TB now exceed those due to HIV infection (1.5 million vs 1.2 million in 2014 according to WHO).

The WHO, the Centers for Disease Control and Prevention (CDC), and professional societies have recommended targeted testing and treatment of high-risk individuals with latent TB infection as part of an effort to eliminate TB in the United States. The newly released guidelines from the USPSTF published in *JAMA* recommend screening for latent TB infection in primary care settings,

But the *JAMA* editorial notes that the USPSTF excludes the highest-risk populations (persons living with HIV, close contacts of persons with active TB, and those being treated with immunosuppressive agents) from its review of evidence for screening for latent TB infection in primary care settings because TB screening and treatment of latent TB infection may already be considered standard of care in these groups.

New tools are needed to help define which patients with latent TB infection outside these epidemiologically defined groups are at high risk

for progression. The editorial also notes other challenges in dealing with latent TB infection such as the need for new, shorter and less toxic regimens for the treatment of latent TB infection given that less than 50 percent of patients complete treatment for latent TB infection. Furthermore, there need to be further efforts to avoid testing low risk persons given that this results in many false-positive diagnostic test results.

Further guidance for clinicians (from the CDC and state and local health departments) is needed to implement these USPSTF recommendations in primary care settings, note the authors. Given that the highest-risk groups 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.

In the short run, say the authors, implementation science (operational research) will be needed to help facilitate the best ways of implementing the USPSTF recommendations for TB screening in primary care settings. In the long run, overcoming the challenge of latent TB infection will require substantial investments in TB research by foundations and by the U.S. and other governments from high- and middle-income countries.

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