Screening for Latent Tuberculosis Infection
Dick Menzies, MD

The US Preventive Services Task Force (USPSTF) has recommended screening of adults at increased risk for latent tuberculosis (TB) infection (LTBI). This recommendation (B statement) is based on an evidence review that found that available tests—in particular, the tuberculin skin test and interferon-γ release assays—were sufficiently accurate to identify persons with LTBI and that TB preventive treatment (TPT) regimens now recommended in the US should provide moderate net benefit to persons identified from screening. The USPSTF advised following the recommendations for testing in persons who have immunosuppression made by the American Thoracic Society and Centers for Disease Control and Prevention 2017 and recommendations for TPT made by the Centers for Disease Control and Prevention in 2020. The USPSTF noted that this recommendation is for adults not included in other recommendations for LTBI testing and treatment, such as persons living with HIV, persons about to receive a solid-organ transplantation or tumor necrosis factor-α inhibitors, or other groups at increased risk because of immune suppression. The task force also noted that this recommendation is not for contacts of persons with a recent diagnosis of active TB disease, who are generally investigated by public health services. Hence, these recommendations are focused on persons who are otherwise healthy but have increased likelihood (risk) of having TB infection. Although this includes some US-born persons, the vast majority of persons who will be affected by this recommendation are individuals who immigrated to the US from countries where TB incidence is much higher. On the basis of estimates of the prevalence of LTBI among persons in the US who were born outside the US, this represents a very substantial increase from the number of persons now screened.

Before starting screening, a reminder is needed. The USPSTF also recommends that to achieve the benefit of screening, it is important that persons who screen positive for LTBI receive follow-up and treatment; if TPT is not completed, then there will be no benefit of screening. Hence, a decision to implement screening for LTBI in any setting or for any population must include a commitment to ensure adequate follow-up of those with positive test results. This includes medical and radiographic evaluation to exclude TB disease, offering TPT to all those who are eligible, and then education and counseling plus subsequent close follow-up of those who accept TPT, to ensure adherence as well as to detect and manage any adverse effects. Substantial time and resources are needed to ensure that care is well organized for all steps in the cascade to minimize losses, or a screening program will have far less benefit than expected. Numerous studies have shown that there are substantial losses in the cascade of LTBI care, at the steps of initial identification of candidates for screening (testing), medical evaluation, and offering TPT, as well as acceptance and completion of TPT by individuals, particularly in studies evaluating large-scale programs. These studies have shown that the majority of losses in the cascade occur before starting TPT. Shorter TPT regimens will do little to correct these losses, yet evidence reviews and guidelines fail to account for these problems when evaluating net benefit. The USPSTF evidence reviewers could not find any randomized clinical trials that directly compared the health benefits or harms of LTBI-screened populations with unscreened populations, meaning that no trial has evaluated the full cascade of care from screening to TPT completion. However, intervention studies have shown that problems causing cascade losses can be identified and corrected, thereby enhancing the number of eligible persons who initiate and complete TPT. In addition, observational studies have demonstrated that in well-organized programs more than 50% of those potentially eligible have completed TPT.
How can the expanded screening be achieved, particularly given the requirement for expanded capacity for all subsequent cascade steps? In 2006, Sterling et al. estimated that between 291,000 and 433,000 individuals initiated treatment for LTBI in the US and Canada, but only 2% of them were treated in private practice; more than 90% were treated in publicly funded clinics. Subsequent surveys noted that 17% of persons recommended to start TPT never did, and of those who did start, less than 50% completed. On the basis of these findings, one can roughly calculate that only approximately one-third of this large population actually benefited from TPT. Further expansion of screening will identify many more individuals who should be treated, but gains may be limited without ensuring better acceptance and completion.

We suggest that the focus of screening this large and otherwise healthy population should be shifted to primary care, clearly an underutilized sector for TB prevention in the US and Canada. A modeling study concluded this could have a major impact on TB incidence in California. In the UK, immigrants undergo LTBI screening at the time of registration for primary care. In a retrospective analysis of 368,097 eligible immigrants who registered in primary care, 37,268 (10.1%) underwent LTBI screening, of whom 66,40 (17.8%) were positive, and 17,40 (26.2%) started TPT. Even though the proportion of eligible migrants who were tested was low, and the proportion of those testing positive who started treatment was also low, programmatic LTBI testing and treatment at primary care registration was effective at diagnosing active TB earlier and lowered the long-term risk of TB.

In an 11-year retrospective cohort study of 59,007 recent immigrants to Leicestershire, UK, who registered for primary care, 60% of all TB cases were potentially preventable if they had been screened and tested at that time.

Integration of LTBI screening into primary care has the potential to be more effective as care for LTBI is integrated with other primary care services and acceptance and adherence of TPT are enhanced by a stable, long-term patient-practitioner relationship. This may also be more feasible and cost-effective because it would avoid the creation or expansion of a parallel system of public health clinics. This would also facilitate repeated attempts to screen and treat; individuals who do not complete screening and/or TPT immediately could be reminded in subsequent years.

What is needed for successful implementation of LTBI screening in primary care? First, simple and accurate screening tests are needed. Both tuberculin skin test and interferon-γ release assay would appear to qualify, although the interferon-γ release assays may be easier in office-based practice if other laboratory tests must be performed in outside facilities.

Second, TPT should be short, simple, and very safe. Ideally, the regimen should be safe enough that no monitoring is required except to bolster adherence. Self-administered therapy may be more feasible in many settings and populations, particularly office-based practice. The currently recommended regimens of 4 months of daily self-administered rifampin and 3 months of weekly isoniazid rifapentine (3HP) have very low rates of hepatitis in trials, and even lower rates in observational studies, although approximately 5% of persons will stop the 3HP regimen because of the occurrence of a flu-like syndrome that can be serious occasionally.

Third, services need to be reimbursed. Reimbursement for preventive services is not a trivial issue, although the grade B classification by the USPSTF for this recommendation facilitates private insurers' reimbursement.

In summary, the basic conditions of simple tests and safe treatment appear to be met for widespread implementation of LTBI screening in high-risk populations in primary care settings, but this would require a paradigm shift away from public clinics to primary care. Are primary care practitioners ready? Some studies suggest they are not. The needs and optimal strategies to integrate LTBI care into primary care have not been well studied. More than 50 years after LTBI screening and treatment were first widely recommended and implemented, there is still remarkably little evidence about implementing LTBI diagnosis and treatment in primary care in North America.

The available tests and treatment are appropriate for primary care; it is hoped that reimbursement mechanisms are also available in most settings. What is still needed is evidence that
this is feasible and that retention of individuals throughout the LTBI cascade of care is high, from initial identification, screening, evaluation, and initiation to completion of TPT. In this way, the full benefits of LTBI screening will be realized for individuals and the long-term goal of TB elimination in the US may be achieved.

ARTICLE INFORMATION
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Corresponding Author: Dick Menzies, MD, McGill TB Centre, Montreal Chest Institute and the Research Institute of the McGill University Health Centre, 5252 de Maisonneuve West, Room 3D.58, Montreal, QC H4A 3SS, Canada (dick.menzies@mcgill.ca).

Author Affiliation: McGill TB Centre, Montreal Chest Institute and the Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.

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REFERENCES


