Draft Research Plan

Latent Tuberculosis Infection in Adults: Screening

March 11, 2021

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In an effort to maintain a high level of transparency in our methods, we open our Draft Research Plan to a public comment period before we publish the final version.

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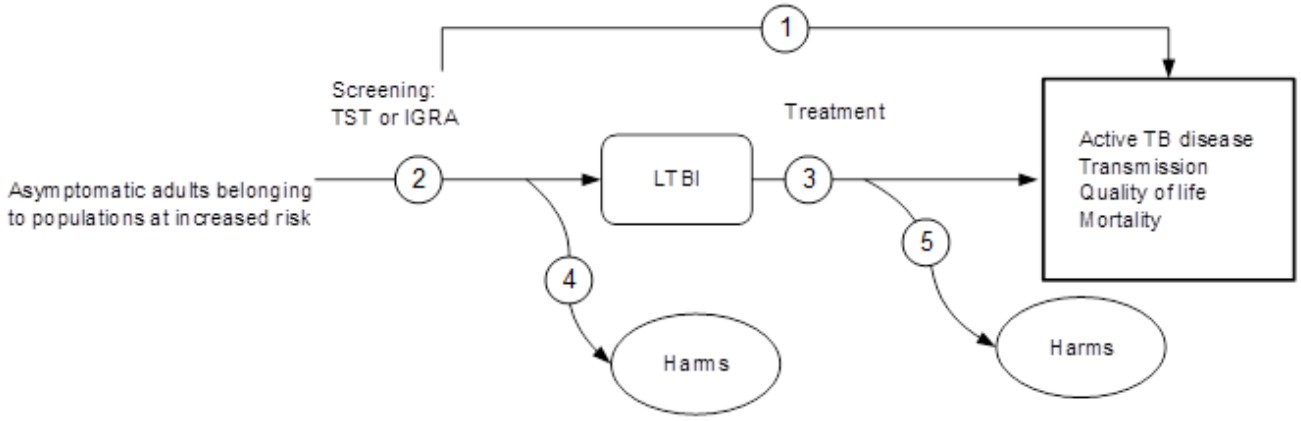
Proposed Analytic Framework



Abbreviations: IGRA=interferon gamma release assay; LTBI=latent tuberculosis infection; TB=tuberculosis; TST=tuberculin skin test.

Proposed Key Questions to Be Systematically Reviewed

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1. Is there direct evidence that targeted screening for latent tuberculosis infection (LTBI) in primary care settings in asymptomatic adults at increased risk for developing active tuberculosis (TB) disease improves quality of life or reduces active TB disease incidence, transmission of TB, or disease-specific or overall mortality, including among specific

populations of interest?
2a. What are the accuracy and reliability of the tuberculin skin test (TST) or interferon gamma release assay (IGRA) for screening in asymptomatic adults who are at increased risk for developing active TB disease, including among specific populations of interest?
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 TB disease, including among specific populations of interest?
3. Does treatment of LTBI with Centers for Disease Control and Prevention (CDC)–recommended pharmacotherapy regimens improve quality of life or reduce progression to active TB disease, transmission of TB, or disease-specific or overall mortality, including among specific populations of interest?
4. What are the harms associated with screening for LTBI, including among specific populations of interest?
   a. Do these harms differ by screening method or strategy?
   b. 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?

Proposed Contextual Question

The contextual question will not be systematically reviewed and is not shown in the Analytic Framework.

1. What risk assessment tools are available for use in primary care to identify adults to screen for LTBI?

Proposed Research Approach

The proposed Research Approach identifies the study characteristics and criteria that the Evidence-based Practice Center will use to search for publications and to determine whether identified studies should be included or excluded from the evidence review.

Criteria	Included	Excluded

Criteria	Included	Excluded
Populations	**All KQs:** A priori subgroups of interest include those defined by age, sex, race/ethnicity, pregnancy, and higher risk for developing TB.* For each KQ, we will look for evidence to inform whether results differ by subgroups. **KQs 1, 4:** Asymptomatic adults belonging to populations at increased risk for LTBI.* Studies that combine eligible and ineligible populations can be included if results are stratified for the eligible portion of the study population or the ineligible portion does not exceed 25% of the study population. **KQ 2:** For sensitivity outcome: Patients with bacteriologically confirmed active TB who have not yet received treatment or who had received no more than a few weeks of treatment. For specificity outcome: Healthy persons with no history of TB exposure or risks. Studies that combine children and adults or studies with both HIV-negative and HIV-positive persons (sensitivity outcome only) can be included if results are stratified for the eligible portion of the study population or the ineligible portion does not exceed 25% of the study population. **KQs 3, 5:** Asymptomatic adults with confirmed LTBI (e.g., with a positive TST and without symptoms or chest x-ray findings indicative of active TB disease); otherwise, same criteria as for KQ 1 except that close contacts of active TB patients are eligible if LTBI is confirmed.	**KQs 1, 4:** Children, symptomatic adults, close contacts of active TB patients, and populations at highest risk for progression from LTBI to active TB disease because of underlying immunosuppression or for whom LTBI screening and treatment would be part of standard disease management by specialty care providers. This includes persons with HIV, head and neck cancer, leukemia or lymphoma, silicosis, history of or planned organ transplant, dialysis, planned or active use of TNF-α inhibitors, and planned or active use of chemotherapy. **KQ 2:** For sensitivity outcome: Persons with TB infection not confirmed by culture, AFB smear, or molecular tests. For specificity outcome: Persons with known history of TB or TB exposure, persons with HIV, and acutely ill persons.

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Criteria	Included	Excluded
Intervention and Comparator	**KQs 1, 4:** Screening with TST, IGRA, or both compared with no screening. **KQs 2, 4:** TST using Mantoux method with intermediate strength dose of PPD and standard thresholds for positive test (i.e., 5 mm, 10 mm, or 15 mm). Commercially available, FDA-approved IGRA tests: T-SPOT.*TB*, QFT-Gold in tube (QFT-GIT 3rd generation), and QFT-Gold Plus (4th generation). **KQs 3, 5:** Treatment with CDC-recommended regimen (INH daily for 6 or 9 months, INH twice weekly by directly observed therapy for 6 or 9 months, RIF daily for 4 months, or INH plus RPT weekly by directly observed therapy for 3 months) compared with placebo, no treatment, delayed treatment, or another eligible treatment.	**KQs 1, 4:** Studies with no comparator group. **KQs 2, 4:** Other tests, such as nucleic acid amplification and two-step TST. **KQs 3, 5:** Studies comparing other treatments or combinations (i.e., regimens that are not recommended by CDC).
Outcomes?	**KQs 1, 3:** Active TB disease, TB transmission, quality of life, and mortality (disease-specific and overall). **KQ 2:** Sensitivity, specificity, and reliability (i.e., test-retest). **KQ 4:** False-positive results leading to unnecessary testing or treatment, labeling, stigma, anxiety, and cellulitis. **KQ 5:** Hepatotoxicity, mortality from hepatotoxicity, nausea, vomiting, peripheral neuropathy, development of drug-resistant TB, and other specific adverse effects of medications.	**KQ 2:** Concordance rates among tests and other outcomes.
Study Designs?	**KQ 1:** RCTs, prospective cohort studies. **KQ 2:** RCTs, cohort studies, cross-sectional studies. **KQ 3:** Systematic reviews and meta-analyses (including network meta-analyses),‡ RCTs. **KQ 4:** Systematic reviews, RCTs, and prospective cohort studies **KQ 5:** Systematic reviews and meta-analyses (including network meta-analyses), RCTs, prospective cohort studies, and case-control studies.	All other study designs not already indicated.

Criteria	Included	Excluded
Setting?	**KQ 1:** Study settings considered to be applicable to primary care, including homeless shelters, correctional facilities, college health settings, long-term care facilities, and public health clinics. **KQ 2:** Any setting. **KQs 3, 5:** Same as KQ 1, except that workplace settings are also eligible. **KQ 4:** Studies eligible for KQs 1 or 2.	**KQs 1, 3, 5:** HIV and subspecialty care settings and workplace settings that screen for LTBI as part of a formal surveillance program for occupational exposure.
Country	**KQs 1, 3, 5:** Countries categorized as "Very High" on the Human Development Index, as defined by the United Nations Development Programme. **KQ 2:** For sensitivity outcome: Studies in any country. For specificity outcome: Studies in intermediate- or low-TB–burden countries. **KQ 4:** Studies eligible for KQs 1 or 2	**KQs 1, 3, 5:** Countries not categorized as "Very High" on the Human Development Index, as defined by the United Nations Development Programme. **KQ 2:** For specificity outcome: Studies in high-TB–burden countries.†
Quality?	Studies rated good or fair quality?	Studies rated poor quality
Language?	Full text published in English?	Not English language?

* Adult population subgroups at increased risk for developing active TB include 1) persons who have immigrated from TB-endemic countries; 2) persons who work or reside in facilities or institutions with high-risk individuals, such as homeless shelters, correctional facilities, nursing homes, and residential facilities; and 3) persons with increased risk for progression from LTBI to active TB because of underlying illness or use of medications, injection drug use, or radiographic evidence of prior healed TB.[1]

† High–TB-burden countries include the following: Angola, Bangladesh, Brazil, Cambodia, Central African Republic, China, Congo, the Democratic Republic of the Congo, Democratic People's Republic of Korea, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Nigeria, Pakistan, Papua New Guinea, Peru, the Philippines, the Russian Federation, Somalia, South Africa, Thailand, the United Republic of Tanzania, Vietnam, and Zimbabwe. This list is not exhaustive but represents the countries with the highest absolute burden (high rates and high population).[2]

‡ We will focus on the best evidence to address this KQ on treatment, focusing on the most recent high-quality meta-analysis rather than re-reviewing and synthesizing the primary RCTs that were summarized in the prior review on this topic (e.g., those comparing INH vs. placebo that were published in the 1960s and 1970s).

Abbreviations: AFB=acid fast bacilli; CDC=Centers for Disease Control and Prevention; FDA=Food and Drug Administration; HIV=human immunodeficiency virus; IGRA=interferon gamma release assay; INH=isoniazid; KQ=key question; LTBI=latent tuberculosis infection; PPD=purified protein derivative; QFT=QuantiFERON; RCT=randomized, controlled trial; RIF=rifampin; RPT=rifapentine; TB=tuberculosis; TNF-α=tumor necrosis factor-α; T-SPOT. *TB*=commercial IGRA assay; TST=tuberculin skin test.

References

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1. World Health Organization. Tuberculosis Data. https://www.who.int/teams/global-tuberculosis-programme/data. Accessed February 18, 2021.
2. Centers for Disease Control and Prevention. Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. https://www.cdc.gov/tb/publications/LTBI/default.htm. Accessed February 18, 2021.

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