Tuberculosis Control in RI: Maintaining Control Efforts in the Context of Declining Incidence and Funding for Tuberculosis Programs

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INTRODUCTION

Tuberculosis (TB) infection is one of the most common infections in the world, affecting an estimated one-third of the world’s population and accounting for 1.3 million deaths annually. Incidence in the United States (US) peaked most recently in 1992 at 26,673 cases (10.4 cases per 100,000 persons), which was associated with the emergence of the HIV epidemic together with declines in funding for TB control in the 1980s. Tuberculosis incidence has since declined, with only 9,945 cases reported in 2012 (3.2 per 100,000). Sixty-three percent of TB cases in 2012 occurred among foreign-born populations. In Rhode Island (RI), highest rates are seen among persons from Guatemala (23%), Dominican Republic (15%), and Cambodia (15%). Multi-drug resistant tuberculosis, defined as resistance to isoniazid and rifampin, has been reported in 1% of US TB cases consistently. Though pulmonary TB is most common, disease can occur throughout the body with diverse manifestations.

Tuberculosis is spread by persons with pulmonary disease. Following initial infection within the lungs, the infection is usually contained and the mycobacteria remain quiescent within granulomas, a state termed latent tuberculosis infection (LTBI). Ten percent of infected persons subsequently develop TB over the course of their life, with half of that risk occurring within the first 2 years after infection. For persons with HIV, the risk of reactivation is higher and may reach 10% per year. Though eradication of infection may be possible, this cannot be confirmed with current testing and the assumption is made that all those infected are at risk for reactivation disease. Predictive models have been developed to estimate the risk of TB and of treatment complications with risk calculators available online.

Tuberculosis control involves the combination of active case finding for TB disease, assurance of adequate treatment for active disease with directly observed therapy (DOT), screening and treatment of TB infection among contacts to infectious cases, and targeted testing and treatment of LTBI among higher risk populations. This combined strategy has contributed to the substantial declines in reported TB.

Support for TB control has varied historically with increased support following times of higher incidence and declines when incidence diminishes. In 2000, the Institute of Medicine (IOM) report Ending Neglect highlighted the impact of declines in US categorical funding for TB on disease control and outlined key recommendations for improvements with the goal of TB elimination. It was estimated that 4 times the current funding of $528 million annually would be required to fully implement the IOM recommendations. Despite this, federal funding for TB control has been level or declining when adjusted for inflation since 1994, with greater reductions in funding for lower-incidence states.

Given ongoing funding gaps, partnerships with other programs and primary care providers are needed to maintain TB control efforts. With increases in federal support for community health centers (CHC), these centers may be model partners in this work. In 2012, a framework was established in RI under the direction of the RI Department of Health (HEALTH) to promote community-based testing and LTBI treatment by starting with CHC primary care providers. In this article we review the elements of screening and treatment for LTBI, discuss challenges implementing these in a community-based setting, and provide recommendations for providers to support integration of LTBI treatment into community care programs.

Diagnosis of Latent TB Infection

The Centers for Disease Control (CDC) recommends targeted testing for persons at high risk for TB with the framework that a decision to test is a decision to treat. Testing is recommended for persons who are at increased risk of exposure [e.g. persons from high-burden countries, contacts to persons with pulmonary TB] or persons at increased risk for reactivation disease [e.g. persons with HIV or on immunosuppressive medications]. Given the role of the CHCs in serving immigrants, these sites and similar primary care practices are important for targeted testing.

Historically, the cornerstone of screening for TB infection has been the tuberculin skin test (TST). This test has been validated in large cohorts with long-term follow-up such that evidence-based recommendations for interpretation of results for most individuals can be provided. A key limitation of the TST has been the potential for false positives due to exposure to either BCG vaccine or non-tuberculous mycobacteria. This potential is highest among young persons with recent BCG administration.

Interferon Gamma Release Assays (IGRAs) were developed as more specific alternatives to TST, without cross-reactivity with BCG or common nontuberculous mycobacteria. Two forms of IGRA have been approved for use, the
QuantiFERON®-TB Gold, which is used most commonly, and the T-SPOT®-TB test. These assays have been validated with short-term follow-up of populations at high risk for disease with performances comparable to TST. False negatives and false positives, however, can occur. For persons tested with both TST and an IGRA, the interpretation of discordant results may not be clear.12-14 CDC guidelines discourage the use of dual testing except in limited circumstances, principally:

1) When increased sensitivity for detection of TB infection is desired and treatment would be recommended based on positivity of either test.

2) When a confirmatory test is necessary to persuade a patient to take treatment due to skepticism regarding the interpretation of the TST.8

Given the potential for false positive TSTs for persons with a history of BCG, the recommendation is that IGRA should not be used as the sole test.

Uncertainty exists with regard to the management of persons with a history of BCG or no clear exposures to TB who test positive by TST. The core recommendation is that testing be restricted to persons of sufficiently high risk that a positive test would be accepted as indication to treat. Though not endorsed by the guidelines, in practice IGRA testing has been used as a second test in low-risk individuals for whom false positive TST is likely. Because the sensitivity of the IGRA is not 100%, individuals with TB infection may be misclassified based on a negative IGRA and not offered treatment. IGRA should not, therefore, be used as a second test in those at high risk for development of tuberculosis disease.

Diagnosis of LTBI requires exclusion of TB disease. Historically, about one-third of patients with active TB identified at the RISE TB Clinic were identified as part of initial evaluation for LTBI. Standard protocols include conducting a symptom screen and obtaining a chest x-ray. Symptom screens focus on the most common symptoms including fever, cough, unintentional weight loss, and drenching night sweats. These screens may miss extrapulmonary TB and so the initial evaluation needs to include review of other unexplained symptoms the patient may have that may be attributable to TB.

**Treatment of Latent TB Infection**

There are several approved regimens for the treatment of LTBI (see table 1). The oldest and best studied is therapy with isoniazid. The treatment course is 9 months and, if gaps occur, a total of 270 doses must be received within a period of 12 months. Liquid formulations are available but the sorbitol base limits tolerability at doses greater than 50mg. Isoniazid has the advantage that it has few drug interactions and serious toxicities are relatively rare.15 The common side effects include inflammation of the liver, with the incidence of serious toxicity estimated to be as low as 0.1 to 0.6% of cases. Drug-induced neuropathic pains of the extremities can occur and are often preventable with vitamin B6 supplementation.

Shorter course treatment with rifampin has been both validated independently and tested compared to isoniazid.16-18 Completion rates were better with rifampin and tolerance was higher. Hepatotoxicity can occur, though it is thought to be less frequent than with isoniazid. The relative risk of grade 3 or 4 hepatotoxicity was 0.12 for rifampin.16 Hypersensitivity reactions and hematologic changes, principally thrombocytopenia and leukopenia can occur but are rare.

The third regimen is the combination of isoniazid and rifapentine dosed weekly as DOT for 12 weeks.19,20 This regimen was validated for use in contacts to persons with pulmonary TB. Dosing for both agents is weight-based. This regimen is recommended for patients of age 12 or higher with high risk of disease based on recent exposure, documented conversion of TST or IGRA.

Whichever regimen is used, treatment monitoring and documentation of treatment outcome is a key component of therapy. Adherence assessment is necessary and where possible documentation of the number of doses received and the time period should be made. Persons who subsequently require immunosuppressive therapy may require retreatment if sufficient documentation of treatment adequacy is not available.

**Latent Tuberculosis Infection in Rhode Island**

RI is a low-incidence state for TB with 23 cases reported in 2012.21 On average, more than 60% of cases occur among foreign populations. A National Health and Nutrition Examination Survey (NHANES) survey from 1999-2000 estimated the prevalence of LTBI at 4.2% nationwide with 18.7% prevalence among the foreign born.21 The 4.2% overall prevalence would suggest that approximately 44,000 people in RI

**Table 1. Treatment Regimens for Latent Tuberculosis Infection**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Duration</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>10 mg/kg children, 5 mg/kg adults. Max dose 300 mg/day</td>
<td>9 months</td>
<td>Daily: 270 within 12 months Twice Weekly DOT: 76 within 12 months</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>10 mg/kg. Max dose 600 mg/day</td>
<td>4 months</td>
<td>Daily: 120 within 6 months</td>
</tr>
<tr>
<td><strong>Isoniazid + rifapentine</strong></td>
<td>INH: 15mg/kg round up to nearest 50 or 100mg. Max dose: 900mg. RPT: 10.0-14.0 kg 300 mg 14.1-25.0 kg 450 mg 25.1-32.0 kg 600 mg 32.1-49.9 kg 750 mg ≥ 50.0 kg 900 mg</td>
<td>3 months</td>
<td>Weekly DOT: 11 or 12 within 16 weeks</td>
</tr>
</tbody>
</table>
are living with LTBI. Though LTBI has been reportable since 2010, it remains underreported and LTBI targeted testing expansion is needed to reach more high-risk individuals.

Funding for TB control in RI has decreased overall in the last 10 years, reaching its current nadir in 2012. Given these declines, the TB control program has prioritized:

1) Identification and medical treatment of active cases
2) Contact investigations and treatment of LTBI among contacts to actives
3) Evaluation and treatment of TB infection among persons at high risk of reactivation
4) Evaluation and treatment of TB infection among persons with no other access to services

The tuberculosis control program at HEALTH works in partnership with the Miriam Hospital RI RISE Clinic, which provides consultation and treatment services, and with Hasbro Children’s Hospital for treatment of LTBI among children in RI. In 2013, there were 27 confirmed active TB cases in RI and the TB program identified 1,183 contacts to active cases and performed 5,056 DOT visits. During the same period, 413 LTBI cases were identified and managed at the Hasbro Children’s Hospital and RI RISE TB Clinics. The overall completion rate for persons starting on LTBI treatment at RISE in 2013 was 67%.

The proposed framework to collaborate with CHCs for treatment of LTBI included CHCs consulting the RISE Clinic to conduct an initial evaluation to exclude active TB and set an LTBI treatment plan. Given the high risk of reactivation disease among persons with HIV, all persons without prior documented HIV testing and those with risk factors for recent HIV exposure would be screened as part of the initial RISE clinic evaluation. Low-risk LTBI patients who are able to receive treatment through the CHC would be referred back for the treatment and monitoring. In addition to contacts to persons with active TB, high risk or complex LTBI patients, particularly young children, persons with HIV, and those who are on or who are candidates for immunosuppressive therapy, would complete their treatment course at the RISE Clinic.

Several barriers were noted with the initial roll-out of this program. Medication costs and costs of associated monitoring for patients without insurance historically have been borne by the state and the Miriam Hospital. Patients referred back to CHCs without medication coverage were unlikely to receive the full treatment course in the absence of financial supports. Access to insurance under the Affordable Care Act has improved access to medications and diagnostics for some, though immigrants may be excluded and cost-share requirements continue to pose barriers. Without specific funding and mechanisms to support the costs of treatment for the uninsured, referral to the CHC would result in failure to treat.

Provider comfort with both medication management and clinical monitoring is equally a challenge. Many providers have rarely, if ever, prescribed TB medications and may be uncomfortable managing the side effects and toxicities. Though targeted education can address these concerns, a high level of commitment from CHCs is needed to maintain investment in the program over time.

The referral step before treatment creates the potential for loss to follow-up. This may be particularly a concern if there is inadequate tracking of referrals. If new symptoms develop during the period prior to follow-up for treatment, health center providers may be uncomfortable treating or providing the needed clinical reassessment. If treatment complications occur, explicit planning is needed to determine when referral to RISE Clinic is appropriate. Further solidification of this model is needed with the eventual goal of expanding to additional pediatric and adult primary care providers.

**RECOMMENDATIONS**

In order for a community-based treatment for LTBI to succeed there are several key areas that need to be addressed:

- Increased targeted testing is needed among high-risk groups.
- Use of IGRA per recommendations to minimize referrals due to false positive TSTs.
- Ongoing education of community providers is needed to improve knowledge of tuberculosis and the treatment of LTBI.
- Partnering primary care providers, starting with CHCs, need to develop internal processes for tracking prescriptions/adherence.
- Continued support for LTBI treatment at the Rise and Hasbro clinics is needed both for high-risk patients and to serve those without adequate coverage for treatment in the community.
- Treatment completion rates and complications need to be reviewed focusing on gaps or adverse outcomes resulting from the referral process.

**References**


