Moving toward Tuberculosis Elimination
Implementation of Statewide Targeted Tuberculin Testing in Tennessee

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Rationale: From 1993 to 2010, annual U.S. tuberculosis (TB) rates declined by 58%. However, this decline has slowed and disproportionately occurred among U.S.-born (78%) versus foreign-born persons (47%). Addressing the high burden of latent TB infection (LTBI) must be prioritized.

Objectives: Only Tennessee has implemented a statewide program for finding and treating people with LTBI. The program was designed to address high statewide TB rates and growing burden among the foreign-born. We sought to assess the feasibility and yield of Tennessee’s program.

Methods: Analyzing data from the 4.8-year period from program inception in March 2002 through December 2006, we quantified patients screened using a TB risk assessment tool, tuberculin skin tests (TST) placed and read, TST results, and patients initiating and completing LTBI treatment. We then estimated the number needed to screen to find and treat one person with LTBI and to prevent one case of TB.

Measurements and Main Results: Of 168,517 persons screened, 102,709 had a TST placed and read. Among 9,090 (9%) with a positive TST result, 53% initiated treatment, 54% of whom completed treatment. An estimated 195 TB cases were prevented over the 4.8 years analyzed, and program performance measures improved annually. The number of TSTs placed to prevent one TB case ranged from 150 for foreign-born persons to 9,834 for persons without TB risk.

Conclusions: Targeted tuberculin testing and LTBI treatment is feasible and likely to reduce TB rates over time. Yield and cost-effectiveness are maximized by prioritizing foreign-born persons, a large population with high TB risk.

Keywords: latent tuberculosis; mass screening; emigrants and immigrants

In the United States, reported cases of tuberculosis (TB) decreased by 58% from the resurgence peak in 1992 to 2010 (1). However, this reduction occurred disproportionately within the U.S.-born population (75%) compared with the foreign-born population (47%) (1). As a result, the proportion of reported TB cases in the United States occurring among foreign-born persons has increased from 29 to 61%, and the current rate of TB is approximately 11 times greater among foreign-born versus U.S.-born persons (1, 2). Because most TB occurring among foreign-born persons is due to reactivation of latent TB infection (LTBI) as opposed to recent community transmission (3–6), concerted efforts to address the burden of LTBI, especially the high burden in foreign-born persons, are essential for TB elimination (7–11).

LTBI treatment is generally safe and effective in preventing TB disease (12, 13) and can be cost saving in certain high-risk populations (14–21). Targeted testing of high-risk persons such as the foreign-born who would benefit from LTBI treatment has been recommended for more than a decade but is not widely implemented (7–9, 22–25). Some community settings or localities have implemented targeted testing activities, but there are no published examples of a statewide program. Additionally, the benefit of LTBI treatment among many programs is
hindered by low levels of treatment initiation and completion (7, 26–30).

When the Centers for Disease Control and Prevention (CDC) released targeted testing guidelines in 2000, Tennessee’s TB case rate had been above the U.S. rate for nearly 2 decades, and the proportion of foreign-born cases had doubled in only the past 5 years (31). To address this concern, the Tennessee Department of Health (TDOH) obtained state funding to implement a statewide targeted tuberculin testing program. Following national recommendations, Tennessee’s program objectives were to screen persons at high risk for TB, including the foreign-born; limit tuberculin skin testing (TST) of low-risk persons; and prevent TB disease through successful initiation and completion of LTBI treatment among infected persons (2, 7, 32). The program was designed to identify and test high-risk persons already coming to Tennessee’s 95 county health departments for public health services, such as immunization; communicable disease screening; Women, Infants, and Children; Early Periodic Screening, Diagnosis, and Treatment; as well as at community sites such as places of employment, worship, and other high-yield locations. A novel risk assessment tool was developed to identify persons at high risk for TB or LTBI, as previously described (32). Trained public health staff conduct skin testing using the Mantoux method (33), and TDOH TB clinics provide clinical evaluation and treatment for LTBI according to national standards (7, 34). To determine the feasibility and potential impact of a statewide targeted testing and treatment initiative, we evaluated the outcomes of Tennessee’s program from implementation March 1, 2002 through December 31, 2006. Some data included in this manuscript were presented in abstract form (35).

METHODS

Definitions

Persons with any risk factor for TB exposure or progression to active TB once infected are considered “high risk” for TB and all others are considered “low risk.” (7, 32) Individuals born outside the United States, Western Europe, Canada, Australia, New Zealand, and Japan are considered high-risk “foreign-born” regardless of duration of U.S. residence (9, 23, 32). A positive TST result is defined according to CDC recommendations (7). TDOH TB clinics dispense LTBI therapy 1 month at a time. We define treatment initiation as having received at least 1 month’s supply of LTBI treatment. Treatment completion is defined as having received at least 6 to 9 months of isoniazid within a 12-month interval, 4 months of rifampin within a 6-month interval, or having “treatment completed” documented in the TDOH database (7, 32). A prevented TB case was one that would have occurred had LTBI not been diagnosed and treated.

Data Analysis

Statewide risk assessment data (demographics, TB risk factors, TST results, symptoms, and HIV risk data), TB or LTBI diagnosis, and treatment information are entered into a single program database (7, 32). After excluding patients with TB disease and persons who had a documented prior positive TST result or had already completed LTBI treatment, we determined the number of patients screened with the risk assessment tool, TSTs placed and read, TST results, and initiation and completion of LTBI treatment. To evaluate program progress over time, we stratified analyses by year. To assess program yield and impact, we calculated the number of TSTs placed to find one case of LTBI each case. Denominator for latent tuberculosis infection (LTBI) treatment was 3,600, as it includes only 2002–2005. TST = tuberculin skin test.

Economic Analysis

Although a formal economic analysis was not done as part of this evaluation, the overall program cost was calculated, including start-up costs (personnel, data management, program coordination) and ongoing costs (including annual program coordination, screening, evaluation for TB disease, LTBI treatment, and managing medication-related side effects). We used this to obtain a crude estimate of the cost per case of TB prevented.

Ethical Review

CDC and TDOH determined this study was a public health program evaluation and did not constitute human subjects research.

RESULTS

Overall Yield of Tennessee’s Targeted Testing and Treatment Program

From March 1, 2002 through December 31, 2006, 168,517 patients were screened with the TB risk assessment tool (Figure 1). Approximately 95% of these were screened at health departments throughout Tennessee, whereas the remaining patients were targeted through community outreach (data not shown). A total of 125,200 TSTs were administered, of which 91,332 (73%) were given to high-risk persons (Figure 1). Out of 102,709 persons with recorded TST results, a total of 9,090 (9%) had a positive result and 4,780 (53%) of these initiated treatment. From 2002 to 2005, 1,953 of 3,600 (54%) completed treatment.

Data regarding Tennessee’s overall program yield by risk assessment classification are shown in Table 1. Although only 17% of TSTs were given to foreign-born persons, the proportion of positive TST results was substantially higher among this group compared with non–foreign-born and low-risk persons (33 vs. 5 and 1%, respectively). In addition, a much larger proportion of foreign-born persons initiated (57%) and completed treatment (57%) during the program compared with high-risk persons. The overall yield of program from implementation March 1, 2002 through December 31, 2006, 168,517 patients were screened with the TB risk assessment tool (Figure 1). Approximately 95% of these were screened at health departments throughout Tennessee, whereas the remaining patients were targeted through community outreach (data not shown). A total of 125,200 TSTs were administered, of which 91,332 (73%) were given to high-risk persons (Figure 1). Out of 102,709 persons with recorded TST results, a total of 9,090 (9%) had a positive result and 4,780 (53%) of these initiated treatment. From 2002 to 2005, 1,953 of 3,600 (54%) completed treatment.

Figure 1. Yield of program, 2002–2006. Total numbers are given along with relevant proportion, using the previous bar as the denominator in each case. Denominator for latent tuberculosis infection (LTBI) treatment completion is 3,600, as it includes only 2002–2005. TST = tuberculin skin test.
TABLE 1. IMPACT AND YIELD OF PROGRAM BY RISK ASSESSMENT CLASSIFICATION, 2002–2006

<table>
<thead>
<tr>
<th>Risk</th>
<th>Screened for TB</th>
<th>TST Placed, n (%)</th>
<th>TST Result Recorded, n (%)</th>
<th>TST-Positive, n (%)</th>
<th>Started LTBI Treatment, n (%)</th>
<th>Completed LTBI Treatment, through 2005, n (%)</th>
<th>Lifetime Risk of TB (%)</th>
<th>Estimated TB Cases Prevented</th>
<th>NNT to Find One LTBI</th>
<th>NNT to Prevent One TB Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign-born</td>
<td>28,322</td>
<td>21,680 (77)</td>
<td>17,699 (82)</td>
<td>5,759 (33)</td>
<td>3,269 (57)</td>
<td>1,416/2,484 (57)</td>
<td>6.7–8.6</td>
<td>112–144</td>
<td>4</td>
<td>150–193</td>
</tr>
<tr>
<td>High risk, non-foreign-born</td>
<td>85,342</td>
<td>69,652 (82)</td>
<td>57,860 (83)</td>
<td>2,933 (5)</td>
<td>1,334 (45)</td>
<td>474/980 (48)</td>
<td>5.7–7.1</td>
<td>33–41</td>
<td>24</td>
<td>1,702–2,120</td>
</tr>
<tr>
<td>Low risk</td>
<td>54,583</td>
<td>33,868 (62)</td>
<td>27,150 (80)</td>
<td>398 (1)</td>
<td>177 (44)</td>
<td>63/136 (46)</td>
<td>4.7‡</td>
<td>3</td>
<td>85</td>
<td>9,834</td>
</tr>
<tr>
<td>Total</td>
<td>168,517</td>
<td>125,200 (74)</td>
<td>102,709 (82)</td>
<td>9,090 (9)</td>
<td>4,780 (53)</td>
<td>1,953/3,600 (54)</td>
<td>6.3–7.9</td>
<td>147–184</td>
<td>14</td>
<td>680–851</td>
</tr>
</tbody>
</table>

Definition of abbreviations: LTBI = latent tuberculosis infection; NNT = number needed to test with tuberculin skin test; TB = tuberculosis; TST = tuberculin skin test.

* Risk adjusted for age, size of TST reaction, and risk factors (29). Calculation, including sensitivity analysis, described in methods. Multiplying this percentage by the number of patients with a positive TST result gives the total number of lifetime cases of TB expected from that TST-positive population if no treatment is provided. Expected number of cases is as follows: foreign-born: 386–495; high-risk non–foreign-born: 167–208; low-risk: 19; total: 573–718.

1 Described in Methods. Uses estimated lifetime risk of TB and actual proportion initiating and completing treatment for each risk classification and assumes 90% efficacy of isoniazid for those who complete treatment.

2 By definition, low-risk patients have no exposure risk factors, so there is no range in the sensitivity analysis.

Economic Analysis

The calculated age-, size of TST induration-, and risk-factor–adjusted lifetime risk of TB for our population was 7.9% (28). Based on this, 718 cases of TB disease would be expected from the 9,090 persons with a positive TST result. Based on actual program treatment initiation and completion rates and an assumed 90% treatment efficacy, the program prevented 184 of these cases through LTBI treatment. If the expected treatment initiation and completion targets were met (75% for each), the number of TB cases prevented would increase to 364. One case of TB was prevented for every 679 TSTs placed. The number of TSTs placed to prevent one case of TB disease decreased from 771 in 2002 and 1,051 in 2003 to 530 in 2005. Results of the sensitivity analysis for each year are shown in Table 2. The number of TSTs placed to prevent one case of TB varied by risk group, ranging from 150 for foreign-born persons to 9,834 for low-risk persons (Table 1).

The total program cost from initiation through 2006 (including start-up costs, and applying the 2006 completion rate of 54.25%) was $6.4 million, of which approximately $800,000 was in start-up and annual management costs, $3.1 million was in screening costs, and $2.5 million was in LTBI treatment costs (including management of adverse effects). Overall, the crude (undiscounted) cost per case of TB disease prevented was $34,800.

DISCUSSION

Although addressing the burden of LTBI and thereby preventing new cases is essential for U.S. TB elimination (7, 8, 11), only Tennessee has implemented a statewide program to find and treat patients with LTBI. An estimated 184 lifetime TB cases were prevented over the program’s first 5 years. Continued targeted testing activities should further reduce the 250 to 300 TB cases reported in Tennessee annually. Although outcomes from the program’s second 5 years have not yet been fully analyzed, the latest reported TB case rate for Tennessee represents an historic low of 3 per 100,000 persons in 2010 (well below the U.S. rate of 3.6 per 100,000) (1). When the program started, TB rates in Tennessee were above the national average. To what extent the targeted testing program may have contributed to this success is not known, but it may have been an important contributor. The actual impact on the TB epidemic in Tennessee would also depend on migration patterns, including interstate migration. However, the demonstration that a program...
that addresses the LTBI burden in the highest-risk populations can prevent many cases of TB will inform national approaches to TB elimination. At a national level, a Tuberculosis Epidemiologic Studies Consortium study estimated that between 4,000 and 11,000 active TB cases could be prevented through LTBI treatment in 1 year, most of which is provided at local health departments (25). Together, these data indicate a substantial community-level benefit from the large-scale provision of LTBI therapy.

Tennessee’s program also demonstrates the feasibility and high yield of a statewide approach. By integrating the targeted testing initiative with routine public health services at the health department and select community sites, Tennessee’s program screened more than 168,000 persons for TB risk from 2002 to 2006. Nearly 10,000 persons with positive TST were identified, and approximately 2,600 persons completed LTBI treatment, thereby reducing both their individual risk of future TB as well as their risk of spreading the disease to others (7, 8, 11, 40). However, Tennessee’s program also demonstrates that the yield of screening varied substantially by risk group. The number needed to test to prevent one TB case among foreign-born persons is more than 60-fold lower than low-risk persons and more than 10-fold lower than non–foreign-born high-risk persons. Nearly one-third of foreign-born persons with skin tests placed and read had a positive TST result, and initiation and treatment rates were highest among this group. This is consistent with national data highlighting the very high TB risk among foreign-born persons and strongly suggests that this population target will likely maximize the number of cases prevented for the resources invested (9, 23, 41, 42).

Tennessee’s experience also shows that additional efforts are needed to maximize TB prevention. Despite improvements over time, the large number of foreign-born persons who were not screened when accessing care at the health department represents a missed opportunity to prevent additional TB cases. The foreign-born population in Tennessee increased from 160,000 in 2000 to 265,000 in 2009, just over 10,000 per year (43), further highlighting the need to scale up screening in foreign-born populations. Doing this within current funding levels may be feasible (27, 39, 44, 58, 59). Although no data before program implementation are available to enable a direct before-and-after comparison, both yield and efficiency increased over the first 5 years of targeted screening and treatment activities. Between 2002 and 2006, there was a 36% decrease in the proportion of low-risk persons tested, from 74 to 47%. In addition, Tennessee substantially increased the number of foreign-born persons and high-risk non–foreign-born persons screened during that same interval. As a result of this heightened focus on high-risk persons, the number of persons tested to diagnose one person with LTBI decreased by 20%, from 15 in 2002 to 12 in 2006. Likewise, the number of persons tested needed to prevent one case of active TB disease decreased substantially. This improved efficiency over time has increased the overall impact and program yield, thereby enhancing effective use of limited program resources. Greater focus on the highest-risk populations (foreign-born), continued efforts to minimize testing of low-risk populations, and improved treatment initiation and completion would result in

### TABLE 2. YIELD AND IMPACT OF PROGRAM BY YEAR, 2002–2006

<table>
<thead>
<tr>
<th>Year</th>
<th>Screened for TB Risk</th>
<th>TST Placed, n (%)</th>
<th>TST Read, n (%)</th>
<th>Positive TST Result, n (%)</th>
<th>Initiated LTBI Treatment, n (%)</th>
<th>Completed LTBI Treatment, n (%)</th>
<th>Estimated TB Cases Prevented</th>
<th>NNT to find One LTBI</th>
<th>NNT to Prevent One TB Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>25,156</td>
<td>20,285 (81)</td>
<td>15,905 (78)</td>
<td>1,315 (8)</td>
<td>756 (57)</td>
<td>370 (49)</td>
<td>21–26</td>
<td>15</td>
<td>771–967</td>
</tr>
<tr>
<td>2003</td>
<td>29,953</td>
<td>23,305 (78)</td>
<td>18,452 (79)</td>
<td>1,440 (8)</td>
<td>582 (40)</td>
<td>312 (54)</td>
<td>18–22</td>
<td>16</td>
<td>1,051–1,317</td>
</tr>
<tr>
<td>2004</td>
<td>37,290</td>
<td>23,730 (82)</td>
<td>18,864 (8)</td>
<td>928 (50)</td>
<td>516 (56)</td>
<td>297 (57)</td>
<td>43–54</td>
<td>12</td>
<td>794–995</td>
</tr>
<tr>
<td>2005</td>
<td>38,985</td>
<td>28,426 (73)</td>
<td>24,080 (85)</td>
<td>2,389 (10)</td>
<td>1,334 (56)</td>
<td>755 (57)</td>
<td>43–54</td>
<td>12</td>
<td>530–664</td>
</tr>
<tr>
<td>2006</td>
<td>37,133</td>
<td>24,066 (85)</td>
<td>20,542 (10)</td>
<td>1,180 (57)</td>
<td>478 (53)</td>
<td>1,953 (54)^1</td>
<td>147–184^4</td>
<td>14</td>
<td>679–852</td>
</tr>
<tr>
<td>Total</td>
<td>168,517</td>
<td>125,200 (74)</td>
<td>102,709 (82)</td>
<td>9,090 (9)</td>
<td>4,780 (53)</td>
<td>1,953 (54)^1</td>
<td>147–184^4</td>
<td>14</td>
<td>679–852</td>
</tr>
</tbody>
</table>

For definition of abbreviations, see Table 1.

* Denominator for total LTBI completion is 3,600, as it includes only patients initiating treatment in 2002–2005.

^1 Extrapolated to include 2006, using mean treatment completion of 54.25% for treatment completion.
a continued decline in the number of persons tested to prevent a case.

A case of drug-susceptible TB in the United States costs approximately $4,000 to treat if hospitalization is not required and $19,000 if hospitalization is needed (approximately 50% of patients are hospitalized) (60). With costs of contact investigations and treatment of secondary cases, costs can be as high as $38,550 per case (61). The estimated crude cost per case of TB disease prevented in this program was just under $35,000. This is not a formal cost-effectiveness analysis and does not take into account discounting for cases prevented later in life. A more comprehensive cost-effectiveness analysis is beyond the scope of this report and will be published at a later date, but our data suggest that cost-effectiveness of such programs would vary substantially depending on what population the program focuses, which again emphasizes the need for the program to target its interventions to the highest-risk groups. With greater (possibly even nearly exclusive) focus on the foreign-born population, which has the highest prevalence of LTBI, the highest LTBI treatment initiation and completion rates, and the smallest estimated number needed to test to prevent one case of TB, additional cost-effectiveness gains should be feasible. Cost per TB case prevented could also be reduced through improved treatment initiation and treatment completion rates (55, 57, 62, 63). Of note, a recently completed clinical trial demonstrated that a 3-month regimen of once-weeklyisoniazid and rifapentine was as safe and effective as daily isoniazid monotherapy for 9 months and was associated with improved adherence rates (53). It is also possible that the substitution of interferon-γ release assays (IGRAs) for TST could improve cost-effectiveness. Although not recommended for LTBI diagnosis at the time Tennessee’s program was implemented, IGRAs such as the QuantiFERON-TB Gold In- Tube test (QFT-GIT) and T-SPOT.TB test (T-Spot) are now approved by the U.S. Food and Drug Administration. Although there is no gold standard for LTBI diagnosis, IGRAs have an advantage over the TST because these tests require a single patient visit, results are not “boosted” by subsequent testing, and previous bacille Calmette-Guérin vaccination does not cause a false-positive IGRA test result (64). IGRAs may even be cost-effective compared with TST in some settings in spite of increased cost of testing (42, 65, 66).

This analysis is subject to certain limitations. We applied a single estimate of 90% efficacy for anyone who collected 100% of their assigned LTBI treatment and 0% efficacy to patients who initiated treatment but did not meet this criterion. In reality, efficacy may be lower for persons completing regimens other than 9 months of isoniazid. On the other hand, patients who did not complete but took some of their LTBI treatment would actually have some efficacy. Because most patients were prescribed 9 months of isoniazid, we believe the possible overestimate of efficacy in some patients is likely offset by assuming no benefit from persons who took partial therapy. Also, we could not measure treatment adherence other than number of months dispensed or documentation of “treatment completed” by a provider. Although our analysis includes only patients treated within this public sector program and not private practice or other nonpublic health providers, the results may be applicable to other settings where patients at risk for TB, including foreign-born patients, present for routine care. Evaluating the feasibility of an LTBI testing and treatment program in such settings may be warranted. Last, although public health staff has been asked to report persons newly identified with active TB through program activities, this guidance was not consistently followed, and we are unfortunately unable to accurately report or even estimate these data.

The identification and treatment of latent infected persons to prevent new TB cases is both effective and feasible within the setting of a statewide public health program. As of 2010, there were almost 40 million foreign-born persons living in the United States, of whom approximately 20 to 30% likely have LTBI (32, 67, 68). Prioritizing this population for testing and LTBI treatment is approximately 10-fold higher yield than non–foreign-born high-risk patients and more than 60-fold higher yield than focusing on low-risk patients, which would result in the most efficient use of limited public health resources for reducing TB incidence and ongoing Mycobacterium tuberculosis transmission in the community. Other states, cities, or public health jurisdictions with a large population of foreign-born residents should strongly consider the establishment of a large-scale targeted testing program prioritizing this group. Strategies to optimize LTBI treatment initiation and completion among persons infected with M. tuberculosis are essential for the ultimate goal of TB elimination.

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References


