Comparison of an ESAT-6/CFP-10 Peptide-Based Enzyme-Linked Immunospot Assay to a Tuberculin Skin Test for Screening of a Population at Moderate Risk of Contracting Tuberculosis\textsuperscript{V}

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Received 8 February 2007/Returned for modification 20 March 2007/Accepted 10 April 2007

Screening for latent tuberculosis infection (LTBI) with the Mantoux tuberculin skin test (TST) has many limitations including false-positive results due to Mycobacterium bovis bacillus Calmette-Guérin (BCG) vaccination. Three hundred ninety adult inmates with normal screening chest radiographs in a county jail were evaluated for LTBI using TST and an ESAT-6/CFP-10 peptide-based enzyme-linked immunospot assay (T-SPOT.TB). LTBI prevalence rates were 19.0% and 8.5% by T-SPOT.TB and TST, respectively. Overall agreement between test results was 82.8% (\( \kappa = 0.29 \)). Positive T-SPOT.TB results were significantly associated with increased age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01 to 1.06) and intravenous drug use history (OR, 2.92; 95% CI, 1.36 to 6.27). Positive TST results were significantly associated with increased age (OR, 1.06; 95% CI, 1.02 to 1.09) and foreign birth (OR, 6.61; 95% CI, 1.98 to 22.01). Discordant covariates between the assay results included increased age (OR, 0.96; 95% CI, 0.94 to 0.99) and intravenous drug use history (OR, 0.41; 95% CI, 0.19 to 0.88). T-SPOT.TB reactivity is unaffected by prior BCG vaccination. T-SPOT.TB may be more sensitive than TST in diagnosing LTBI among a moderate risk population of inmates, particularly those with intravenous drug use history. Longitudinal studies are needed to assess the positive predictive value of T-SPOT.TB in identifying those most likely to convert to active disease in general populations as well as in high-risk subpopulations.

Among adults, tuberculosis (TB) is the world’s foremost cause of death from a single infectious agent (20). In the United States, new TB cases continue to be reported in all states, with a significant proportion of these cases from correctional facilities (5). Transmission of TB in correctional facilities has been documented by several studies and represents a public health problem not only for the inmates and employees of these facilities but also for the communities in which they reside (3, 10).

The tuberculin skin test (TST) is currently the standard method of screening for latent TB infection (LTBI) in the United States despite its limitations, which include the need for at least two patient contacts, uncertainty about the immune status of the person tested, false-positive results because of cross-reactivity with Mycobacterium bovis bacillus Calmette-Guérin (BCG) vaccine and mycobacteria other than \( M. \) tuberculosis, technical difficulties in administering the test, and errors related to subjectivity in reading the results (1, 2, 12).

The recent advent of a rapid technique for detecting antigen-specific gamma interferon (IFN-\( \gamma \))-producing T-lymphocyte cells from peripheral blood offers a new approach for detecting \( M. \) tuberculosis infection (22). The ex vivo enzyme-linked immunospot (ELISPOT) assay for IFN-\( \gamma \) (T-SPOT.TB) counts individual stimulated Th1-type T cells specific for early secretory antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens that are present in \( M. \) tuberculosis but absent from BCG and most environmental mycobacteria (13). When people become infected with \( M. \) tuberculosis, T cells become sensitized to ESAT-6 or CFP-10 antigens in vivo. When these T cells reencounter these antigens ex vivo in the overnight T-SPOT.TB assay, they release the cytokine IFN-\( \gamma \) (13). After 16 to 20 h of incubation, each such T cell gives rise to a dark spot, which is the “footprint” of an individual \( M. \) tuberculosis-specific T cell. The experimental result is thus the number of spots, which are counted manually or by using an automated reader. ELISPOT assays utilizing ESAT-6 and CFP-10 antigens have been performed on subjects in the general populations in several countries including Canada, England, Germany, India, Italy, South Africa, Switzerland, and Zambia. The purpose of this cross-sectional study was to evaluate the performance of the T-SPOT.TB assay compared to TST for TB screening in a moderate-risk population of a large county jail in the United States.

MATERIALS AND METHODS

\textbf{Study design.} This was a cross-sectional study comparing an ESAT-6-CFP-10 peptide-based T-SPOT.TB assay to TST for TB screening. The Committees for the Protection of Human Subjects at the University of Texas Health Science Center in Houston and Baylor College of Medicine approved the research protocol for this study. All inmates gave written informed consent.

\textbf{Study site and selection criteria.} Adult inmates (\( \geq 18 \) years of age) with normal screening chest radiographs at the Harris County Jail (HCJ) in Houston, Texas, were invited to participate in this study during the months of May through
TABLE 1. Demographics and multivariate logistic regression for concordance between T-SPOT.TB and TST (n = 390)

| Variable                          | No. (% of subjects) | T-SPOT.TB/TST concordancea | Crude OR (95% CI) | Adjusted OR (95% CI) |
|-----------------------------------|----------------------|-----------------------------|-------------------|----------------------|
| Age (per yr increase)             | 390 (100)            | 0.96 (0.94–0.98)*           | 0.96 (0.94–0.99)* |
| Gender                            |                      |                             |                   |                      |
| Male                              | 331 (84.9)           | 1.00                        | 1.00              |
| Female                            | 59 (15.1)            | 0.69 (0.35–1.36)            | 0.73 (0.35–1.51)  |
| Ethnicity                         |                      |                             |                   |                      |
| Caucasian                         | 131 (33.6)           | 1.00                        | 1.00              |
| African-American                  | 166 (42.6)           | 1.01 (0.55–1.84)            | 0.78 (0.41–1.52)  |
| Hispanic                          | 93 (23.8)            | 1.11 (0.54–2.26)            | 0.83 (0.36–1.94)  |
| Birth country                     |                      |                             |                   |                      |
| United States                     | 348 (89.2)           | 1.00                        | 1.00              |
| Other                             | 42 (10.8)            | 0.73 (0.33–1.61)            | 0.72 (0.27–1.91)  |
| Prior incarceration               |                      |                             |                   |                      |
| No                                | 46 (11.8)            | 1.00                        | 1.00              |
| Yes                               | 344 (88.2)           | 1.02 (0.45–2.29)            | 1.03 (0.42–2.50)  |
| Intravenous drug use              |                      |                             |                   |                      |
| No                                | 341 (87.4)           | 1.00                        | 1.00              |
| Yes                               | 49 (13.6)            | 0.41 (0.21–0.80)*           | 0.41 (0.19–0.88)* |
| Lived in shelterb                 |                      |                             |                   |                      |
| No                                | 327 (83.8)           | 1.00                        | 1.00              |
| Yes                               | 63 (16.2)            | 0.54 (0.29–1.03)            | 0.73 (0.36–1.50)  |
| HIV status                        |                      |                             |                   |                      |
| Negative                          | 372 (95.4)           | 1.00                        | 1.00              |
| Positive                          | 18 (4.6)             | 3.67 (0.48–28.04)           | 5.08 (0.64–40.22) |

a, P < 0.05.

b History of living in nursing homes, homeless shelters, drug rehabilitation centers, or “bunkhouses.”

TABLE 2. Concordance and k statisticc for T-SPOT.TB and TST (n = 390)

| TST result | No. of subjects | T-SPOT.TB result of | Total |
|------------|----------------|--------------------|-------|
| Positive   | 20             | 13                 | 33    |
| Negative   | 54             | 303                | 357   |

**RESULTS**

A total of 447 inmates participated in this study and were screened for LTBI by both tests. Of these, 35 subjects (7.8%) left HJC before their TST results were read while 22 subjects (4.9%) had “indeterminate” T-SPOT.TB results. Concomitant TST and T-SPOT.TB results were available for 390 subjects. The average age of the subjects was 33.5 years (±10.8 years). Subjects were predominantly male, African-American, and born in the United States and had a history of prior incarceration (Table 1). Eighteen subjects (4.6%) tested positive for HIV infection. All HIV-positive subjects were TST negative. One HIV-positive subject had a positive T-SPOT.TB result.

Among the 390 eligible subjects with concomitant results for both tests, 74 subjects (19.0%) tested positive by the T-SPOT.TB while 33 subjects (8.5%) tested positive by TST (Table 2). The concordance between the T-SPOT.TB and TST results in this study was 82.8% (95% confidence interval [CI], trained nursing staff at the HJC administered the TST (one-step method) according to the guidelines established by the Centers for Disease Control and Prevention (CDC) (2). Briefly, 0.1 ml of the tuberculin purified protein derivative (TUBERSOL; Aventis Pasteur Limited, Toronto, Ontario, Canada) containing 5 tuberculin units was injected intradermally on the volar surfaces of inmates’ forearms. Forty-eight to 72 hours later, the diameter of the area of induration around the injection site was measured across the forearm and was reported in millimeters. In this study, reactions of 10 mm or greater were considered “positive” except for the HIV-positive subjects, where the cutoff point for “positive” results was set at 5 mm or greater.

Statistical analysis. The primary outcome of this study was the difference in the prevalence of LTBI according to T-SPOT.TB assay and TST as indicated by the frequency of positive results for each test. We then assessed the level of concordance between the results of these two tests. Concordance was calculated as the overall percent agreement between the results of the two assays using two-by-two contingency tables. The strength of this agreement was examined using Cohen’s kappa (κ) with a κ value of >0.75 representing excellent agreement beyond chance, 0.40 to 0.75 representing fair to good agreement beyond chance, and <0.40 representing poor agreement beyond chance (9).

Multivariate logistic regression models were used to identify variables significantly associated with positive results for each assay and those variables associated with discordance between test results.

The independent variables included in the multiple logistic regression models were gender; age; ethnicity; birth country; intravenous drug use; prior incarceration; history of prior positive TST; living in a shelter which included housing in congregate settings such as drug rehabilitation units, “bunkhouses,” nursing homes, etc.; and HIV status. All statistical analyses were conducted using SAS statistical software (version 9.1; SAS Inc., Cary, NC), with 0.05 as the cutoff point for statistical significance. Additional sociodemographic data including height, weight, history of tobacco and alcohol use, and occupational exposure histories were also collected but were not entered into the regression analysis model.
We used multivariate logistic regression models to identify variables that were independently and significantly associated with decreased concordance between the test results. Concordance between the test results was significantly lower with increased age (odds ratio [OR], 0.96; 95% CI, 0.94 to 0.99) and intravenous drug use history (OR, 0.41; 95% CI, 0.19 to 0.88). In other words, subjects with discordant ELISPOT and TST results were older and 2.44 times more likely to have a history of intravenous drug use.

The distribution of concordant and discordant results is depicted in Table 3. For all discordant results, subjects were more likely to be T-SPOT.TB positive/TST negative than TST positive/T-SPOT.TB negative. The highest proportion of discordant results was found among those with a history of intravenous drug use (30%) (Table 3).

We used multivariate logistic regression models to further identify variables that were significantly associated with increased frequency of positive results for each assay. For T-SPOT.TB, positive results were significantly associated with increased age (OR, 1.04; 95% CI, 1.01 to 1.06) and intravenous drug use history (OR, 2.92; 95% CI, 1.36 to 6.27). For TST, positive results were significantly associated with increased age (OR, 1.06; 95% CI, 1.02 to 1.09) and foreign birth (OR, 6.61; 95% CI, 1.98 to 22.01).

**DISCUSSION**

In this study of a population at moderate risk for tuberculosis, rates of prevalence of LTBI were estimated at 19.0% and 8.5% by the T-SPOT.TB and TST, respectively. The 8.5% frequency of positive TST results in this study is consistent with the less-than-10%-positive TST rate among the population of U.S. city and county jail systems according to a recent joint National Institute of Justice/CDC survey (11). This is also consistent with the 9.0% rate of positive TST results in a recent study by Porsa and colleagues at the HCJ comparing TST to another IFN-γ release assay, the QuantiFERON-TB-GOLD (QFT-G) (18). The 4.9% rate of indeterminate T-SPOT.TB results in this study is similar to the 3 to 4.3% rate of indeterminate results from other studies of this assay (7, 8, 14, 17).

Significant differences between the rate of positive T-SPOT.TB results compared to that of TST (19% versus 8.5%, respectively, in this study) have been previously reported in other studies. In a study among a group of immunosuppressed subjects with documented exposure to an index case of TB, the rate of positive T-SPOT.TB assay was more than twice the rate for TST, 44.2% versus 17.4%, respectively (17). In another study among contacts with a TB disease case in a residential institution for alcoholics, TST results were markedly more positive than the T-SPOT.TB results (44% versus 15%, respectively). In this study, however, nearly 91% of the
subjects were reported to have been BCG vaccinated (23). As with all other investigations of LTBI screening assays, the obvious question then becomes, “which screening assay is more valid (has better sensitivity and specificity profile)?” Because of the lack of a true “gold standard” for the diagnosis of LTBI, we are left with two options to answer this question. We can either refer to sensitivity studies for patients with known TB disease or compare the various assays based on the clinical and epidemiological characteristics of tested individuals in order to determine which assay agrees most with the likelihood of true TB infection.

In sensitivity studies for patients with known TB disease, sensitivity of the T-SPOT.\textit{TB} assay has been consistently higher than that of TST, ranging from 95.4 to 97.2% for the T-SPOT.\textit{TB} assay compared to 66.7 to 89% for TST (4, 14, 15). In a study at the HCJ involving 20 adult inmates with abnormal screening chest radiographs suggestive of TB, agreement between T-SPOT.\textit{TB} and TST was 95% (0.90) (19). The only discordant result belonged to a patient with negative T-SPOT.\textit{TB} and positive TST results. This patient had three negative sputum smears and cultures for acid-fast bacilli. He was diagnosed with community-acquired pneumonia and treated accordingly with success. Even though this was a very small sample, these findings supported the evidence from other studies for patients with active TB, suggesting a better sensitivity and specificity profile for T-SPOT.\textit{TB} than for TST.

In order to determine the possible sources of the observed differences in the rate of positive T-SPOT.\textit{TB} results compared to that for TST in this study, we looked for variables that were associated with statistically significant discordance between the results of these two tests. We then examined the variables that were associated with statistically significant increases in the rates of positive results for each assay. Additionally, we briefly compared our results to our findings from a previous study using QFT-G (18). In our population, only age and history of intravenous drug use were significantly associated with positive T-SPOT.\textit{TB} assay results (Table 4). Older age and foreign birth were significantly associated with positive TST results (Table 4). Older age and history of intravenous drug use were significantly associated with discordance between the T-SPOT.\textit{TB} assay and TST results. Of note, reported history of previous contact with known cases of TB disease had no association with positive results for either test (data not shown). We believe this finding is most likely due to a lack of validity of this historical variable. Subjects often guess about their prior TB contact, and in a majority (if not all) of cases regarding remote exposure to a TB case such information cannot be independently verified.

The observed association of older age with increased frequency of positive TST results in this study has been previously reported in other studies (18, 23). While older age had a significant and consistent association with increased frequency

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Variable & \multicolumn{2}{c|}{T-SPOT.\textit{TB}} & \multicolumn{2}{c|}{TST} \\
\hline
 & % Positive (n) & Crude OR (95% CI) & Adjusted OR (95% CI) & % Positive (n) & Crude OR (95% CI) & Adjusted OR (95% CI) \\
\hline
Age & NA\textsuperscript{a} & 1.04 (1.02–1.06)* & 1.04 (1.01–1.06)* & NA & 1.06 (1.03–1.10)* & 1.06 (1.02–1.09)* \\
\hline
Gender & & & & & & \\
Male & 20.3 (15) & 1.00 & 1.00 & 93.9 (31) & 1.00 & 1.00 \\
Female & 79.7 (59) & 1.57 (0.82–3.01) & 1.54 (0.76–3.12) & 6.1 (2) & 0.34 (0.08–1.46) & 0.23 (0.04–1.24) \\
\hline
Ethnicity & & & & & & \\
Caucasian & 29.7 (22) & 1.00 & 1.00 & 21.2 (7) & 1.00 & 1.00 \\
African-American & 43.2 (32) & 1.18 (0.65–2.15) & 1.63 (0.83–3.20) & 45.5 (15) & 1.76 (0.70–4.45) & 2.84 (0.97–8.28) \\
Hispanic & 32.4 (20) & 1.36 (0.69–2.66) & 1.73 (0.76–3.94) & 33.3 (11) & 2.38 (0.88–6.38) & 1.69 (0.46–6.18) \\
\hline
Birth country & & & & & & \\
United States & 82.4 (61) & 1.00 & 1.00 & 63.6 (21) & 1.00 & 1.00 \\
Other & 17.6 (13) & 2.11 (1.04–4.29)* & 2.28 (0.92–5.69) & 36.4 (12) & 6.23 (2.79–13.89)* & 6.61 (1.98–22.01)* \\
\hline
Prior incarceration & & & & & & \\
No & 10.8 (8) & 1.00 & 1.00 & 24.2 (8) & 1.00 & 1.00 \\
Yes & 89.2 (66) & 1.13 (0.50–2.53) & 1.32 (0.53–3.28) & 75.8 (25) & 0.37 (0.16–0.88)* & 0.41 (0.14–1.19) \\
\hline
Intravenous drug use & & & & & & \\
No & 77.0 (57) & 1.00 & 1.00 & 81.8 (27) & 1.00 & 1.00 \\
Yes & 23.0 (17) & 2.65 (1.38–5.09)* & 2.92 (1.36–6.27)* & 18.2 (6) & 1.62 (0.63–4.16) & 2.54 (0.78–8.27) \\
\hline
Lived in shelter\textsuperscript{b} & & & & & & \\
No & 74.3 (55) & 1.00 & 1.00 & 72.7 (24) & 1.00 & 1.00 \\
Yes & 25.7 (19) & 2.14 (1.16–3.94)* & 1.74 (0.87–3.50) & 27.3 (9) & 2.10 (0.93–4.77) & 2.78 (1.00–7.72) \\
\hline
HIV status & & & & & & \\
Negative & 94.6 (35) & 1.00 & 1.00 & 86.4 (19) & 1.00 & 1.00 \\
Positive & 5.4 (2) & 0.24 (0.03–1.84) & 0.16 (0.02–1.33) & 13.6 (3) & 0.001 (0.00–99.9) & 0.001 (0.00–99.9) \\
\hline
\multicolumn{7}{l}{\textsuperscript{a} * \textit{P} < 0.05.} \\
\multicolumn{7}{l}{\textsuperscript{b} History of living in nursing homes, homeless shelters, drug rehabilitation centers, or “bunkhouses.”} \\
\multicolumn{7}{l}{\textsuperscript{c} NA, not applicable.}
\end{tabular}
\caption{Multivariate logistic regression for positive T-SPOT.\textit{TB} and TST results (\textit{n} = 390)\textsuperscript{a}}
\end{table}
of positive results for both the T-SPOT.TB assay and TST, it was also significantly associated with decreased concordance between the results of these tests (OR, 0.96; 95% CI, 0.94 to 0.99). This may indicate a variable effect of age on the results of these two tests. This effect, however, was very small, and therefore any clinical significance of the observed difference between these assays related to older age is unclear and may simply relate to our sample size.

Among the 42 foreign-born subjects in this study, 12 subjects claimed a history of BCG vaccination. All of the 42 foreign-born subjects except for one (born in Haiti) had vaccination scars that were consistent with BCG vaccination scars. Ten U.S.-born subjects also claimed histories of BCG vaccination, all of whom also had vaccination scars compatible with BCG vaccination. This was not surprising to us since studies have shown that self-reporting of BCG vaccination and even checking for BCG vaccination scars are poor indicators of the BCG vaccination status of individuals (16). For these reasons, foreign birth in this study was considered a more accurate estimate of the BCG vaccination status among our subjects and therefore a possible source of false-positive TST results. This concept was supported by our finding that foreign birth had a statistically significant association with positive results for TST but not the T-SPOT.TB assay.

A competing interpretation of the above findings for our foreign-born subjects could be that the T-SPOT.TB assay is less sensitive than TST. Foreign-born subjects in this study were from countries with TB prevalence rates of 25 to 300 per 100,000 population compared to a TB prevalence rate of less than 10 per 100,000 population in the United States (http://www.gobroomecounty.com/safety/PrevalenceOfTBWorldMap2001.pdf). This distinction, however, becomes irrelevant in large U.S. correctional facilities, where TB prevalence has been estimated at severalfold higher than that in the U.S. general population and up to 200 per 100,000 population (6, 21). Furthermore, and as discussed above, sensitivity of the T-SPOT.TB assay has been consistently reported to be higher than that of TST in studies among subjects with known TB disease.

Other than age, which was associated with increased rate of positive results for both tests, history of intravenous drug use was the only variable that was associated exclusively with increased rate of positive T-SPOT.TB results and decreased concordance between the results of T-SPOT.TB and TST. A closer examination of the data revealed that a history of intravenous drug use was reported by 13% of the U.S.-born inmates and only 0.6% of the foreign-born inmates. To our knowledge, this is the first published report of significant differences between the T-SPOT.TB and TST for LTBI screening in subjects with intravenous drug use history. The HIV-seronegative injection drug users are considered at high risk for developing TB disease once infected and as such are included as a priority group in the targeted tuberculin testing program recommendations by the CDC (2). Among our 18 HIV-positive subjects the only discordant result was due to a T-SPOT.TB-positive/TST-negative situation. Even though this sample of 18 HIV-positive subjects is far too small of a sample to draw statistical or clinical conclusions from, this result is in agreement with a growing number of studies pointing to the efficacy of the T-SPOT.TB assay for LTBI screening among IV-positive or otherwise immunosuppressed individuals (4, 7, 8, 15, 17). The statistically significant association of intravenous drug use history with positive T-SPOT.TB assay results and not positive TST results may indicate the presence of a clinically significant immunosuppressed status in this population. If this is the case, the relative inability of TST to correctly identify the LTBI status of subjects with intravenous drug use history is a source for major concern. This is particularly true in a correctional facility setting, where a disproportionate number of individuals with intravenous drug use histories are congregated.

The overall agreement between T-SPOT.TB and TST in this study (82.8%, $\kappa = 0.29$) is similar to the overall agreement between QFT-G and TST in our previous study at the HCJ (90%, $\kappa = 0.25$) (18). However, the higher rate of positive T-SPOT.TB results compared to that of TST (19% versus 8.5%, respectively) in this study contrasts with our findings in the QFT-G study, where the rate of positive QFT-G results were nearly one-half that of TST (5.4% versus 9.0%, respectively). Possible explanations for the observed differences between T-SPOT.TB in this study and QFT-G in our previous study may include major differences between the population of inmates in this study and our previous study, outbreak of TB at the HCJ in the time period between the two studies, and true differences between the two assays (low sensitivity of QFT-G or low specificity of T-SPOT.TB).

The demographic variables of inmates including age, gender, ethnicity, birth country, and histories of prior incarceration and intravenous drug use were remarkably similar between these two studies (18). Additionally, there have been no known outbreaks of TB disease in recent years at the HCJ. It is therefore very likely that the two new IFN-γ release assays, T-SPOT.TB and QFT-G, in fact measure different things. Similar to QFT-G in our previous study, T-SPOT.TB in this study was unaffected by prior BCG vaccination based on either the reported history of vaccination, the presence of vaccination scar, or foreign birth status as a proxy for BCG vaccination. Association of foreign birth with increased rate of positive TST results in this study is again consistent with the findings in our previous study at the HCJ (18). Unlike T-SPOT.TB in this study, however, the QFT-G response in our previous study at the HCJ appeared diminished in the African-American subjects (18). The majority of our subjects in both studies were African-Americans (42.6% in the present study and 42.3% in our previous study). Additionally, while history of intravenous drug use was associated with statistically significant increase in the rate of positive results with T-SPOT.TB in this study, there was no relationship between intravenous drug use history and QFT-G results in our previous study at the HCJ. Thirteen percent of subjects in both studies had reported history of intravenous drug use. This difference in the responsiveness of T-SPOT.TB and QFT-G in African-American subjects and subjects with intravenous drug use history may be partially responsible for the differences in the rate of positive results between T-SPOT.TB and QFT-G in our studies at the HCJ.

Weaknesses of this study include the cross-sectional study design and the use of a convenience sampling scheme. Additionally, this study suffers from the same major weakness of all studies investigating new diagnostic assays for TB infection, namely, the lack of a true gold standard test, which limits our ability to make unequivocal assessments of the sensitivity and specificity of the new assays compared to TST and to each
other. In the face of our inability to follow individuals at risk for developing tuberculosis, because of the cost and the ethical issues of not treating LTBI suspects, we are left with the option of comparing the new IFN-γ release assays to TST in order to determine which assay agrees most with the likelihood of true TB infection based on the clinical and epidemiological characteristics of individuals.

In summary, our study showed that the new Mycobacterium tuberculosis-specific T-SPOT.TB was unaffected by prior BCG vaccination and that it may be more sensitive than TST in diagnosing LTBI among a moderate risk population of inmates with intravenous drug use history. This is particularly important for individuals with multiple risk factors for TB, who are also at increased risk of false-positive screening results due to prior BCG vaccinations. Additionally, differential responsiveness of T-SPOT.TB and QFT-G in a moderate risk population of correctional facility inmates is intriguing and deserves further evaluation in side-by-side studies. Future prospective studies using disease development as the study end point are required to determine the sensitivity and specificity of the new generation of IFN-γ-releasing assays for TB screening and to elucidate the mechanisms that are responsible for the differences in their levels of responsiveness.

ACKNOWLEDGMENTS

This study was supported in part by Health Resources and Services Administration Bureau of Health Professions grant D14 HP00045 and a grant from Oxford Immunotec, Ltd.

Potential conflicts of interest are as follows. Esmeail Porsa and Edward A. Graviss have received research support from Oxford Immunotec, Ltd. E.A.G. has served as a consultant to Oxford Immunotec, Ltd., and Cellestis, Ltd. The remaining authors of this manuscript do not have a commercial or any other associations that might pose a conflict of interest.

We thank Allison Boyle and Margarita Villanueva for their invaluable contribution to this effort.

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