The Effectiveness of Using Interferon-gamma Release Assays in Screening Immigration Employees for Latent Tuberculosis Infection

MARIE A. DE PERIO, R. TODD NIEMEIER, MATTHEW R. GROENEWOLD

We assessed the prevalence of latent tuberculosis infection in immigration employees and compared two of the screening methods. Using a cross-sectional study design, we administered questionnaires regarding demographics, work, medical history, and tuberculosis risk factors to employees at two immigration facilities. Participants underwent tuberculin skin test (TST) placement and blood collection for the QuantiFERON-TB Gold in-Tube (QFT-GIT) assay. Fifty-four employees underwent QFT-GIT and TST placement. All QFT-GIT results were negative, and three employees tested TST positive. Twenty-three (49%) of 47 employees requiring two-step TST testing underwent second TST placement. Return rates for first and second TST reading were 76% and 74%, respectively. The QFT-GIT completion rate was higher than that for TST (100% vs. 39%, $P < 0.001$). Agreement between TST and QFT-GIT was 94%. Immigration employees had low return rates for their TST reading and second TST placement. Performing the one-visit QFT-GIT has administrative and logistical advantages in this occupational group.
Key words: tuberculosis; tuberculin skin test; interferon-gamma release assay; screening

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INTRODUCTION

It is estimated that one-third of the world's population has latent tuberculosis infection (LTBI), and approximately 5%–10% of those infected will develop active tuberculosis disease within their lifetimes.[1–5] More than 38 million foreign-born persons are currently living in the United States.[6] In 2009, foreign-born persons accounted for 60% of all tuberculosis cases in the United States.[7] The tuberculosis case rate for foreign-born persons is more than 10 times the case rate for US-born persons (18.6 vs. 1.7 cases per 100,000 persons).[7] The tuberculosis case rate among people in custody of US Immigration and Customs Enforcement was found to be 12.5 per 100,000 persons in 2005.[8]

Received from: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH, USA. Send correspondence to: Marie A. de Perio, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, 4676 Columbia Pkwy, R-10, Cincinnati, OH 45226, USA; email: <Mdeperio@cdc.gov>.

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It has been shown that 20%–30% of tuberculosis patient contacts will be found to have LTBI and that approximately 5% of individuals with recently acquired LTBI will develop active tuberculosis disease within two years.[2,10] These data, in conjunction with the higher rates demonstrated among foreign-born persons, suggest that individuals who come into contact with recent entrants into the United States, including immigration workers, are at risk for acquiring tuberculosis.

The 2006 Centers for Disease Control and Prevention (CDC) guidelines for preventing tuberculosis transmission in correctional and detention facilities, which include immigration detention facilities, recommend a comprehensive program of administrative, environmental, and personal respiratory protection controls.[11] One component of tuberculosis control in correctional and detention facilities involves routinely screening workers and inmates for LTBI using the tuberculin skin test (TST) or interferon-gamma release assays (IGRA), and administering isoniazid treatment to those individuals testing positive.

The TST, also known as the intradermal Mantoux test, has been in routine use for diagnosis of LTBI for more than a century.[12] Two-step TST testing is necessary for those employees who have not undergone a TST in more than one year to account for the boosting effect.[13,14]

In 2007, the US Food and Drug Administration (FDA) approved a third-generation IGRA, the QuantiFERON-TB Gold in Tube (QFT-GIT) test (Cellestis Limited, Victoria, Australia), a whole blood IGRA used to diagnose active tuberculosis and LTBI. The QFT-GIT is an enzyme-linked immunosorbent assay test that measures the release of interferon gamma in blood from sensitized persons. The antigens consist of synthetic peptides representing three *Mycobacterium tuberculosis* proteins, ESAT-6, CFP-10, and TB7.7. Blood is incubated with the antigens, and interferon gamma released by sensitized leukocytes is measured.[15] In 2010, CDC guidelines indicated that TSTs and IGRAs (including QFT-GIT) may be used as aids in diagnosing infection with *Mycobacterium tuberculosis*.[16]

Advantages of these IGRAs over the TST include that they necessitate only a single patient visit, results are available in 24 hours, and the findings are not subject to reader bias. The ESAT-6, CFP-10, and TB7.7 proteins are absent from all BCG vaccine strains and from

many nontuberculous mycobacteria.[17] Therefore, among previously BCG-vaccinated and non-BCG-vaccinated subjects, the IGRAs have high specificity.[18–20] Major disadvantages of the IGRAs include their high relative cost and the need for an equipped laboratory.[19] Practical experience in occupational groups other than health care workers is limited.

As part of a health hazard evaluation of their tuberculosis exposure control plans,[21] the objectives of this substudy were to assess the prevalence of LTBI among employees at two immigration facilities using two screening methods: the TST and the QFT-GIT. We also sought to compare the feasibility of both screening methods.

METHODS

In August 2009, we visited two immigration facilities located in the metropolitan Chicago area of Illinois. Both federally operated facilities serve as processing centers for adult immigrant detainees entering federal custody in the Midwestern United States. Each facility processes 100–300 immigrant detainees every week, and one of the facilities houses an immigration court. Detainees are held at the facilities for up to 10 hours and are subsequently transferred to longer-term detention centers where they are housed pending the outcome of their immigration case.

Approximately 120 employees work at both facilities. Most employees work as immigration enforcement agents and detention and deportation officers, who investigate, arrest, detain, and deport undocumented immigrants. These agents and officers have face-to-face contact with undocumented immigrants on a daily basis for up to 12 hours both at the facilities and in transportation vehicles. No physical barriers separating employees from the immigrants exist at the facility in the offices where processing procedures occur or in the majority of transportation vehicles. These agents and officers are frequently away from the facility transporting detainees. Fewer numbers of detention and removal assistants, who provide clerical and administrative support, and supervisory agents and officers work at these facilities. Unlike immigration enforcement agents and detention and deportation officers, they typically spend most or all of their work day at the facilities and tend to have no or less face-to-face contact with immigrants.

We used a cross-sectional study design and invited all employees at each facility to participate in LTBI screening using the TST and the QFT-GIT. After obtaining informed consent, participating employees were asked to fill out a short questionnaire regarding personal characteristics, work history, pertinent medical history, and risk factors for tuberculosis.

Participants who reported a history of a positive TST or LTBI did not undergo further testing and were encouraged to see their primary care physician for annual screening for tuberculosis symptoms. Participants with no such history were asked to provide a blood sample for the QFT-GIT assay and to undergo a TST. We collected whole blood totaling 3 milliliters (mL) into three tubes prefilled with antigen (a negative control tube, a *Mycobacterium tuberculosis*-antigen tube, and a mitogen tube) from each participant. The samples were then transported by courier to the University of Illinois at Chicago reference laboratory where they were analyzed using the QFT-GIT assay and interpreted in accordance with manufacturer guidelines. QFT-GIT results were considered positive if the interferon-gamma level was ≥ 0.35 International Units per mL.

After collecting blood specimens, we immediately placed a TST on each participant. Using the Mantoux method, 0.1 mL of Tuberculin PPD (Tubersol®) was injected intradermally with a syringe and needle. Induration was measured in millimeters by trained nurses after 48–72 hours via standard protocols. If more than one year had elapsed since an employee's last test and if he or she was found to be nonreactive (negative), a second-step TST was placed by the nurse following CDC guidelines.[13,14] The nurses visited both facilities on assigned dates to perform the TST reading on employees, and they were blinded to the results of the QFT-GIT. Induration measuring greater than 10 millimeters (mm) was considered reactive (positive).

Each participant was informed in writing of his or her individual test results and their significance. As a public health response, per the guidelines of Title 45 Code of Federal Regulations Part 46, this clinical evaluation was determined to not require review by an institutional review board.

We calculated the prevalence of LTBI using both screening methods. We also calculated and compared completion rates for each testing method and determined predictors for completion of TST screening through bivariate analyses with SAS 9.2 (SAS Institute, Cary, North Carolina). All statistical tests were two-tailed, with a P value of less than 0.05 considered statistically significant.

RESULTS

Seventy-two (60%) of 120 employees who were working during the site visit, participated in the evaluation. The flow diagram in Figure 1 illustrates the health-hazard evaluation participants and the tuberculosis screening tests.

None of the employees reported a history of active tuberculosis. Seven employees reported a previous history of a positive TST and did not undergo further testing. One employee reported having undergone both the blood test and the TST in the previous week by his personal physician and did not undergo further test-

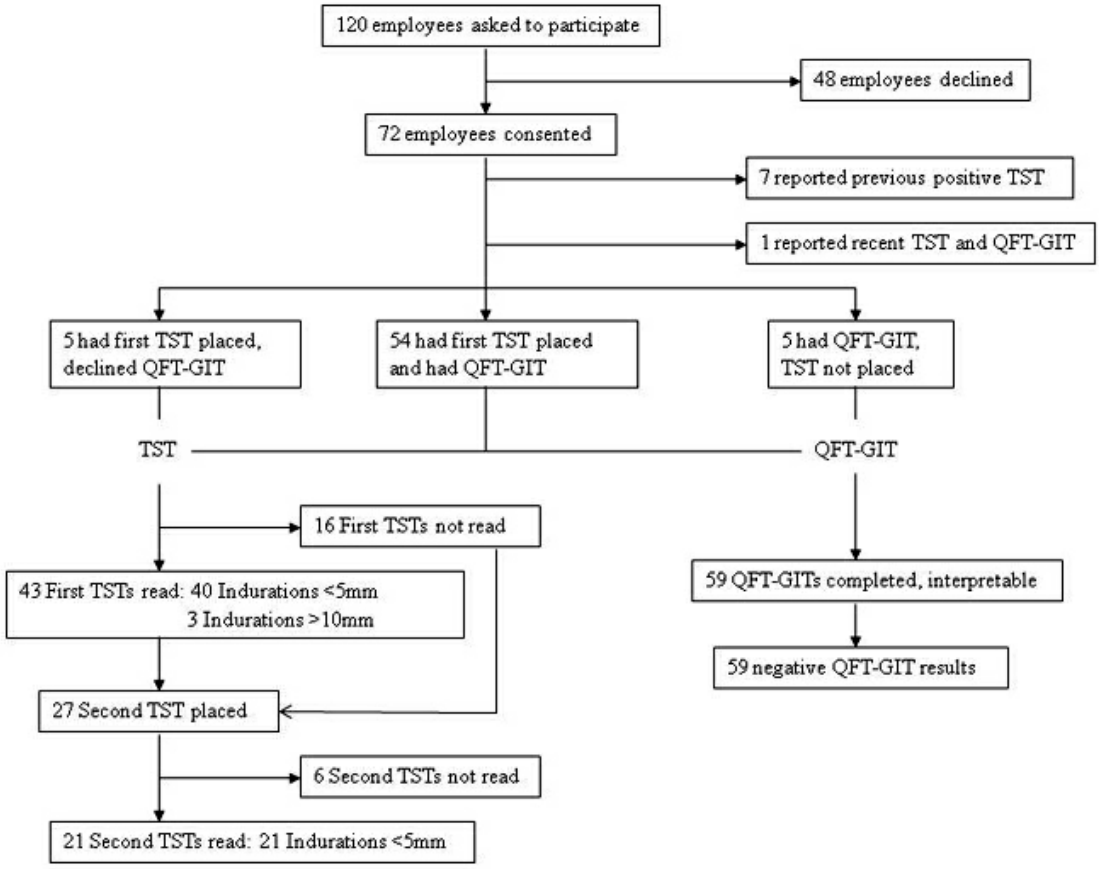

Figure 1—Flow diagram showing the number of health hazard evaluation participants, the tests for LTBI screening they received, and the results.

ing. Fifty-four of the participating employees (75%) underwent blood collection for the QFT-GIT and TST placement. Five employees underwent TST placement but not blood collection, and five employees underwent blood collection for the QFT-GIT but not TST placement. Reasons employees did not undergo TST placement included an inability to return for reading on the assigned date and medical preference. Reasons employees did not undergo blood collection for QFT-GIT included not wanting to have their blood drawn and fear of needles.

The median age for participants was 35 years (range: 22 to 61 years), and the majority (71%) were male. Sixty-two (86%) participants were born in the United States, though 24 (33%) reported having lived outside of the United States. Ten (14%) participants reported having received the BCG vaccine for tuberculosis.

Sixty-eight (94%) participants reported no history of an underlying medical condition associated with a higher risk of progression to active tuberculosis if infected. These medical conditions included diabetes mellitus, silicosis, kidney failure, gastrectomy, cancer, or any immunosuppressive condition.

The median number of years worked at the immigration agency was three years (range: eight months to 30 years). Other work history characteristics of the 72 participants are shown in Table 1.

In total, 67 (93%) participants reported having face-to-face contact with detainees in their current job. Reported job activities included transporting detainees in enclosed vehicles (68%), interviewing detainees (81%), and supervising court visits (31%). Twenty-five (35%) participants reported having had face-to-face contact with a detainee known to have active tuberculosis, while none of the participants reported ever having face-to-face contact with a household member, family member, friend, or other community member known to have active tuberculosis.

As shown in Figure 1, all 59 participants who underwent blood collection for the QFT-GIT had interpretable results, which were all negative. Of the 59 participants who had a first TST placed, 16 (27%) did not return for their first TST reading by the nurse. Of the 43 first TSTs that were read, three (7%) had positive results or indurations greater than 10 mm. Fifty-two (93%) participants required two-step testing, but only 27 (52%) underwent a second TST, and six (22%) did not return for the second TST reading by the nurse. The completion rate for the QFT-GIT was higher than the TST (100% vs. 39%, $P < 0.001$). Among the 41 par-

TABLE 1 Work History Characteristics of Health Hazard Evaluation Participants

Work History Characteristic	No. Participants (%) *n* = 72
Job title	
Supervisor	5 (7)
Immigration enforcement agent	44 (61)
Detention and deportation officer	13 (18)
Detention and removal assistant	7 (10)
Other job title	3 (4)
Previous employment or volunteer work	
Another immigration facility	22 (31)
Correctional facility	26 (36)
Hospital	17 (24)
Nursing home	5 (7)
Homeless shelter	4 (6)

ticipants who completed both the QFT-GIT and the first TST, overall agreement between the TST and QFT-GIT results was 93%. All three participants who had positive TST results had negative QFT-GIT results. No participants had positive QFT-GIT results and negative TST results.

Two of the three participants with positive TST but negative QFT-GIT results were foreign-born and had received the BCG vaccination as children. Though all three participants initially denied having a history of a positive TST, upon further questioning, two did recall having had a positive TST in the past, and one reported a history of taking medication for this for three months. The other participant was uncertain if he had ever had a positive TST. At the time of TST reading, none of the three participants reported any symptoms of active tuberculosis. All three participants were advised to follow up with their primary care physician to discuss treatment.

No differences were present between groups who completed ($n = 22$) and did not complete ($n = 33$) TST screening with respect to sex, country of birth, BCG vaccination, and history of underlying medical condition. Employees who completed TST screening were older (41 years vs. 34 years, $P < 0.01$), and more likely to have ever lived outside of the United States (57% vs. 19%, $P < 0.01$) or to have ever been employed as a detention and removal assistant (22% vs. 3%, $P = 0.03$) than those employees not completing TST screening. Employees who completed TST screening were less likely to be employed as an immigration enforcement agent (48% vs. 78%, $P < 0.01$) or to have previously worked at another ICE facility (9% vs. 36%, $P = 0.01$).

DISCUSSION

Our results show that most employees (93%) participating in our evaluation reported having face-to-face contact with detainees. Though prevalence of LTBI among tested employees was low (0% by QFT-GIT and 7% by TST), many employees participated in job activities that placed them at risk of exposure to tuberculosis, including transporting and interviewing detainees and supervising court visits. While we did not determine the tuberculosis case rates among people in ICE custody at these two immigration facilities, 35% of participants reported having face-to-face contact with a detainee known to have active tuberculosis.

The tuberculosis case rate among people in ICE custody nationwide was estimated at 12.5 per 100,000 persons in 2005.[8] Among all foreign-born populations, tuberculosis rates are highest in the first two years after US entry (75 vs. 16 cases per 100,000 persons).[22] It has also been shown that undocumented foreign-born persons had a longer duration of symptoms before medical evaluation for tuberculosis when compared to US-born persons and documented foreign-born persons.[23] Thus, routine screening of immigration employees for LTBI is necessary.[11]

Our results show that immigration employees had high no-show rates for return reading of TST results, 26% for the first TST and 22% for the second TST. Although the nurses visited both sites for several hours on the assigned reading days, some employees still did not have their TST read. Characteristics associated with having completed TST screening included older age, having lived outside of the United States, and being a detention removal assistant. Detention removal assistants do not typically have job duties requiring them to be out of the office, making it easier for them to be present for all steps of the TST screening process. In contrast, the factor associated with not completing TST screening included being an immigration enforcement agent. These employees spent a significant portion of their work week away from the facility through their involvement in the transportation of undocumented immigrants, which made it more difficult for them to be present for all steps of the TST screening process.

All 59 participants who underwent blood collection for QFT-GIT had interpretable results and completed LTBI screening through that method because only one site visit was required. In contrast, only 23 (39%) participants completed all appropriate steps of LTBI screening through the TST method. To our knowledge, this evaluation is the first to compare the use of IGRAs to the TST for detecting LTBI in immigration employees. Our evaluation demonstrates the feasibility and practicality of performing the QFT-GIT as the LTBI screening method in this population of immigration employees who often have unpredictable schedules. In 2010, CDC guidelines indicated an IGRA (QuantiFERON-TB Gold, QFT-GIT, TSPOT® TB) may be used in place of a TST in all situations in which CDC recommends TST as an aid in diagnosing *Mycobacterium tuberculosis* infection.[16] A major advantage of the QFT-GIT over the TST is that only one employee visit is needed, unlike the TST, which requires two or four

employee visits.[19] Although IGRAs have a higher direct cost per test than the TST, they have been found to be cost-saving and cost-effective tuberculosis screening strategies in populations such as health care workers[24] and contacts of persons with active TB.[25,26] Because five of our participants preferred not to undergo QFT-GIT testing, the TST can continue to be offered as an option for those employees.

Overall agreement between the TST and QFT-GIT results was high at 93%. This is consistent with previous studies that screened Navy recruits (87.7%) and health care workers (96%) for LTBI in the United States.[27,28] Though the kappa statistic is commonly used to measure agreement between tests, we could not calculate it in this evaluation because we found no QFT-GIT results to be positive.

Three employees were found to have discordant results: positive TST but negative QFT-GIT. Upon further questioning, two recalled a previous history of a positive TST and had received the BCG vaccination, and one was uncertain about a history of a positive TST. Because the TST has lower specificity in previously BCG-vaccinated individuals, it is possible these first two employees had false positive results. It has been demonstrated that IGRAs have a higher specificity in BCG-vaccinated subjects compared to the TST because the proteins present in the QFT-GIT test are absent from all BCG vaccine strains.[18–20] This may be one reason these employees were found to have negative QFT-GIT results.

Our evaluation was subject to some limitations. First, our participation rate was 60%, which suggests that compliance with LTBI screening would be suboptimal regardless of the test used. Nevertheless, the completion rate for the QFT-GIT was significantly higher than the TST in our evaluation, and this indicates that compliance could be improved by using the QFT-GIT.

Second, it is possible that we underestimated the true return rate for TST reading in this evaluation had the TST been the sole screening test. Because most of the participants also underwent blood collection for the QFT-GIT test, participants may have chosen not to have their TST read knowing that they'd had another adequate LTBI screening test. While return rates for TST reading among immigration employees have not been described in previous studies, our no-show rates for return reading, 26% for the first TST and 22% for the second TST, were higher than those of health care workers (4%–12%).[29–31] However, participants did not know their QFT-GIT results until both steps were complete, and nurses visited each facility to perform the readings.

Also, we excluded seven employees who reported a history of a positive TST or LTBI from further testing. While offering a QFT-GIT test to these employees may have further documented the usefulness of IGRA testing in this group because IGRAs have been shown to have higher specificity than the TST, studies have shown IFN-γ responses to be variable after treatment.[15,32] Therefore, the significance of the QFT-GIT test result in these employees would not have been certain.

In addition, several unresolved and unexplained issues regarding IGRAs exist. First, the absence of a gold standard for the diagnosis of LTBI can complicate the interpretation of the IGRAs as well as the TST. Second, uncertainty also exists regarding the explanation behind discordance between TST and IGRA results as well as the reproducibility of IGRA results in individual patients.[16,33] Longitudinal studies have revealed fluctuation in IFN-γ responses with serial testing in individual patients.[34–42]

Despite these unresolved issues regarding IGRAs, they are still attractive diagnostic aids for detecting LTBI because they offer administrative and logistic advantages over the TST. Our evaluation demonstrated the feasibility and practicality of performing IGRA testing compared to TST testing in this occupational group. Because IGRAs may be used in place of a TST in all situations in which the TST is used, according to CDC guidelines,[16] we recommended that the immigration facilities consider implementing IGRA testing instead of TST testing. IGRAs should be performed and interpreted according to established protocols using FDA-approved test formats. Additionally, both the standard qualitative test interpretation and the quantitative assay measurements should be reported together with the criteria used for the test interpretation.[16] All employees with positive IGRA results should be referred for a medical and diagnostic evaluation.

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