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Utilization of the QuantiFERON-TB Gold Test in a Two-Step Process with the Tuberculin Skin Test To Evaluate Health Care Workers for Latent Tuberculosis[▽]

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A cost analysis of combining a tuberculin skin test (TST) and the QuantiFERON-TB Gold test (QFT-GT) to detect latent tuberculosis in newly hired health care workers was performed. An approximately 50% reduction in the cost of additional care was realized when workers with positive TST results were subsequently screened using the QFT-GT.

Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide, with 9 million new cases and 2 million deaths reported in 2006 (13, 16). In the United States, 10 to15 million people are estimated to have latent TB (LTB), an infection that is asymptomatic and noninfectious (13). The identification and appropriate treatment of people with LTB is necessary to control TB, since some of these individuals will develop active TB if not properly managed (13).

The tuberculin skin test (TST) was, until recently, the only available method used to detect LTB (2, 4, 5, 7, 10, 14). However, problems are associated with the TST such as a high false-positivity rate, interference by the *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccination and a delayed result which requires two visits to the clinic, one for placement of the TST and another to evaluate the results of testing. This high false-positivity rate also leads to unnecessary procedures such as a chest X-ray (CXR), a more extensive systemic review, and isoniazid (INH) therapy (11, 14).

The QuantiFERON-TB Gold test (QFT-GT; Cellestis Limited, Carnegie, Victoria, Australia) was recently approved by the FDA as a screening test to detect for active TB and LTB (8–11, 16). This assay tests whole blood and uses the enzyme-linked immunosorbent assay format to detect gamma interferon, a cytokine secreted by sensitized T cells in response to specific *Mycobacterium tuberculosis* complex antigens which is absent from the vaccine strain of BCG (8–11, 16). This study was conducted to assess the cost of using a two-step process of evaluating new health care employees with positive TST results with the QFT-GT as a means to eliminate unneeded follow-up and treatment.

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A total of 242 participants presenting to Employee Heath during preemployment screening between April 2006 and April 2008 were enrolled in this study. The ages of the participants ranged from 18 to 64 years, with 141 females and 101 males. Of the participants, 123 were foreign born in third-world countries located in Africa, the Middle East, Southeast Asia, and Central and South America. New employees were asked to complete a questionnaire that included the presence of medical conditions such as human immunodeficiency virus infection, diabetes, chronic pulmonary diseases, and previous TB disease, as well as risk of exposure to TB (such as close contact with patients with active TB or living/traveling in an area where TB is highly endemic), a history of BCG vaccination, and previous TST results. In addition, individuals with previous positive TST results were asked about INH prophylaxis and whether prophylaxis was completed. During this initial screening, a TST was administered and blood was drawn for the QFT-GT. Individuals with a history of a positive TST result were also automatically screened with a CXR. The TST was performed according to the guidelines of the American Thoracic Society and the Centers for Disease Control and Prevention (15). A TST induration or redness of ≥10 mm at 48 to 72 h after tuberculin injection was considered positive. The QFT-GT was performed according to the manufacturer's recommendations.

A positive TST result was identified for 132 (54.5%) of the new employees, with 46 of these also positive by the QFT-GT (Table 1). All other employees who were positive by the skin test were negative by the QFT-GT, while all of the individuals negative by the TST were also negative by the QFT-GT. No changes consistent with TB were detected on the CXR for individuals with a positive TST result. Discrepancies between the TST and QFT-GT results were further evaluated by a comprehensive systematic review. No risk of having LTB was identified in the TST-positive/QFT-GT-negative individuals. All individuals with a positive QFT-GT were evaluated by a pulmonary specialist and offered INH where appropriate. These results showed that, compared with the QFT-GT, the sensitivity and specificity of the TST were 100% and 56%, respectively, with positive and negative predictive values of 34.8% and 100%.

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TABLE 1. Results of screening of new employees with the TST and QFT-GT

No. of employees	Screening result	
	TST	QFT-GT
46	Positive	Positive
86	Positive	Negative
110	Negative	Negative
0	Negative	Positive

New employees with a positive TST result were given information on the pulmonary symptoms of TB and instructed to notify Employee Health if these symptoms were to occur. To assess for long-term outcomes, all TST-positive employees were administered an annual screening test to evaluate for pulmonary symptoms while TST-negative individuals were given an annual TST as part of the routine TB control policy. After a minimum of 18 months, no cases of TB have been identified in this group of patients. Soborg et al. also showed no tuberculous disease in TST-positive/QFT-GT-negative individuals after a follow-up period of 1.5 years (12).

These data demonstrated that the QFT-GT had higher specificity than the TST overall, which agreed with other studies (1, 3, 5, 6, 11). Of interest was that of the 48 individuals who indicated prior BCG vaccination, 38 (82.6%) had a positive skin test result and 13 (28.2%) of these were also QFT-GT positive. In this cohort of new employees tested, the high number of TST-positive or QFT-GT-positive individuals was expected since 50.8% (123/242) of the participants were foreign born in third-world countries.

The estimated original screening cost of using the TST only was $726 ($3 for each participant), followed by TST with reflex of positive individuals to QFT-GT at $8,646 ± $3,960 ($3 for the TST and $60 ± $30 for the QFT-GT for the 132 TST-positive individuals) and QFT-GT alone at $14,520 ± $7,260 ($60 ± $30 for each participant). The evaluation and management of the TST-positive individuals without using the QFT-GT were estimated to cost $86,460 based on a cost of $655 for each person ($70 for a CXR, $450 in health care provider fees [nine visits at $50 each], and $135 in laboratory fees [nine visits at $15 each]), while the management of the 46 individuals with positive QFT-GT results was calculated to cost $30,130 ($655 for each). Overall costs for performing the TST only (TST administration and follow-up evaluation of TST-positive patients) was $87,186, followed by QFT-GT only at $44,650 ± $7,260, and TST with reflex of TST-positive patients to QFT-GT at $38,776 ± $3,960. Thus, this evaluation showed the two-step process of testing using the QFT-GT to further evaluate TST-positive patients showed a reduction in cost of 55.5% compared to use of the TST only. Additional savings not included would be the cost of INH, the patient cost for lost work and travel for clinic visits, and the risk/side effects associated with INH therapy. Other studies have also shown a decrease in the number of candidates requiring INH treatment when the QFT-GT is included in the TB management program (3, 4, 7).

Initial screening with the QFT-GT alone also showed a substantial decrease in cost (48.8%) compared to the TST only. However, this reduction in cost was not as dramatic as that obtained with the two-step process, even in a population where more that 50% of the individuals were TST positive. Methods to reduce the cost of the QFT-GT (such as larger volume testing) will make this screening scenario more attractive, especially in situations where a high TST positivity rate is noted and also in cases where follow-up testing and evaluation of TST results are not as possible.

These data showed that substantial savings could be realized by evaluating employees with a two-step process to detect LTB where a positive TST result is confirmed by the QFT-GT. A long-term assessment of those employees who had a positive TST result and a negative QFT-GT result is currently ongoing to monitor for the potential to develop TB.

REFERENCES

1. **Demkow, U., B. Broniarek-Samson, M. Filewska, K. Lewandowska, J. Maciejewski, K. Zycinska, Z. Zwolska, and J. Kus.** 2008. Prevalence of latent tuberculosis infection in health care workers in Poland assessed by interferon-gamma whole blood and tuberculin skin tests. J. Physiol. Pharmacol. **59**(Suppl. 6):209–217.
2. **de Perio, M. A., J. Tsevat, G. A. Roselle, S. M. Kralovic, and M. H. Eckman.** 2009. Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. Arch. Intern. Med. **169**:179–187.
3. **Diel, R., R. Loddenkemper, K. Meywald-Walter, S. Niemann, and A. Nienhaus.** 2008. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis.* Am. J. Respir. Crit. Care Med. **177**:1164–1170.
4. **Diel, R., A. Nienhaus, and R. Loddenkemper.** 2007. Cost-effectiveness of interferon-gamma release assay screening for latent tuberculosis infection treatment in Germany. Chest **131**:1424–1434.
5. **Harada, N., Y. Nakajima, K. Higuchi, Y. Sekiya, J. Rothel, and T. Mori.** 2006. Screening for tuberculosis infection using whole-blood interferon-gamma and Mantoux testing among Japanese healthcare workers. Infect. Control Hosp. Epidemiol. **27**:442–448.
6. **Kang, Y. A., H. W. Lee, H. I. Yoon, B. Cho, S. K. Han, Y. S. Shim, and J. J. Yim.** 2005. Discrepancy between the tuberculin skin test and the whole-blood interferon gamma assay for the diagnosis of latent tuberculosis infection in an intermediate tuberculosis-burden country. JAMA **293**:2756–2761.
7. **Kowada, A., O. Takahashi, T. Shimbo, S. Ohde, Y. Tokuda, and T. Fukui.** 2008. Cost effectiveness of interferon-gamma release assay for tuberculosis contact screening in Japan. Mol. Diagn. Ther. **12**:235–251.
8. **Kunimoto, D., E. Der, A. Beckon, L. Thomas, M. Egedahl, A. Beatch, G. Williams, G. Tyrrell, R. Ahmed, N. Brown, and R. Long.** 2009. Use of the QuantiFERON-TB Gold test to confirm latent tuberculosis infection in a Canadian tuberculosis clinic. Int. J. Tuberc. Lung Dis. **13**:726–730.
9. **Manuel, O., and D. Kumar.** 2008. QuantiFERON-TB Gold assay for the diagnosis of latent tuberculosis infection. Expert Rev. Mol. Diagn. **8**:247–256.
10. **Marra, F., C. A. Marra, M. Sadatsafavi, O. Moran-Mendoza, V. Cook, R. K. Elwood, M. Morshed, R. C. Brunham, and J. M. Fitzgerald.** 2008. Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts. Int. J. Tuberc. Lung Dis. **12**:1414–1424.
11. **Mazurek, G. H., J. Jereb, P. Lobue, M. F. Iademarco, B. Metchock, and A. Vernon.** 2005. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR Recommend. Rep. **54**(RR-15):49–55.
12. **Soborg, B., A. B. Andersen, H. K. Larsen, K. Weldingh, P. Andersen, K. Kofoed, and P. Ravn.** 2007. Detecting a low prevalence of latent tuberculosis among health care workers in Denmark detected by *M. tuberculosis* specific IFN-gamma whole-blood test. Scand. J. Infect. Dis. **39**:554–559.
13. **Sterling, T. R., J. Bethel, S. Goldberg, P. Weinfurter, L. Yun, C. R. Horsburgh, and the Tuberculosis Epidemiologic Studies Consortium.** 2006. The scope and impact of treatment of latent tuberculosis infection in the United States and Canada. Am. J. Respir. Crit. Care Med. **173**:927–931.
14. **Streeton, J. A., N. Desem, and S. L. Jones.** 1998. Sensitivity and specificity of a gamma interferon blood test for tuberculosis infection. Int. J. Tuberc. Lung Dis. **2**:443–450.
15. **Taylor, Z., C. M. Nolan, and H. M. Blumberg.** 2005. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR Recommend. Rep. **54**(RR-12):1–81.
16. **Veeser, P. I., P. K. Smith, B. Handy, and S. R. Martin.** 2007. Tuberculosis screening on a health science campus: use of QuantiFERON-TB Gold Test for students and employees. J. Am. Coll. Health **56**:175–180.