Published in final edited form as:

Obstet Gynecol. 2011 December ; 118(6): 1363–1370. doi:10.1097/AOG.0b013e31823834a9.

Interferon Gamma Release Assay Compared With Tuberculin Skin Test for Latent Tuberculosis Detection in Pregnancy

Ayaba Worjoloh, MD, MSPH¹, Midori Kato –Maeda, MD², Dennis Osmond, PhD³, Rachel Freyre, BA⁴, Natali Aziz, MD, MS⁵, and Deborah Cohan, MD, MPH⁴

¹Duke University, Hubert-Yeargan Center for Global Health and Department of Obstetrics and Gynecology

²Francis J. Curry National Tuberculosis Center, Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital

³Department of Epidemiology and Biostatistics University of California San Francisco, San Francisco, CA

⁴University of California San Francisco Department of Obstetrics, Gynecology, and Reproductive Sciences

⁵Stanford University School of Medicine, Department of Obstetrics and Gynecology, Stanford, California

Abstract

Objective—To estimate agreement and correlation between the tuberculin skin test and an interferon gamma release assay for detecting latent tuberculosis (TB) infection in pregnant women.

Methods—We conducted a cross-sectional study of pregnant women initiating prenatal care at a university-affiliated public hospital between January 5, 2009 and March 15, 2010. Eligible women received a questionnaire about tuberculosis history and risk factors, as well as the tuberculin skin test and phlebotomy for the interferon gamma release assay. Agreement and correlation between tests were estimated, and different cut-offs for interferon gamma release assay positivity were used to assess effect on agreement. Furthermore, predictors of test positivity and test discordance were evaluated using multivariable analysis.

Results—Of the 220 enrolled women, 199 (90.5%) returned for tuberculin skin test evaluation. Over 70% were Hispanic and 65% were born in a country with high tuberculosis prevalence. Agreement between tuberculin skin test and interferon gamma release assay was 77.39 (k=0.26). This agreement was not significantly changed using different cut-offs for the assay. Birth bacille Calmette-Guérin vaccination was associated with tuberculin skin test positivity (OR 4.33, 95%CI 1.4–13.48, p=0.01), but not interferon gamma release assay positivity. There were no statistically significant predictors of tuberculin skin test and interferon gamma release assay result discordance, however birth in high prevalence country was marginally associated with tuberculin skin test positive and interferon gamma release assay negative results (OR 2.94, 95% CI 0.86–9.97, p=0.08).

Corresponding Author: Deborah Cohan, Department of Obstetrics, Gynecology, and Reproductive Sciences, UCSF, 1001 Potrero Avenue, Ward 6D-22, San Francisco, CA 94110, Tel: 415-206-3658, Fax: 415-206-3112, cohand@obgyn.ucsf.edu.

The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. Cellestis played no role in data collection, analysis, or manuscript preparation.

Financial Disclosure: *The authors did not report any potential conflicts of interest.*

Conclusion—Comparing tuberculin skin test and interferon gamma release assay results in pregnancy, concordance and agreement were poor. Given that much is still unknown about the performance of interferon gamma release assays in pregnancy, further research is necessary before tuberculin skin test is abandoned for screening of latent TB infection in pregnancy.

Introduction

Tuberculosis (TB) infection continues to be a public health issue.(1)

While the incidence of TB infection in the United States has decreased over the past five years, the rate of decline has slowed since 2000.(2) Identifying and treating latent TB infection is a crucial step in the elimination of TB infection in the United States.(3)

Pregnancy represents a unique time to screen for latent tuberculosis in that many high-risk women, including recent immigrants, may present to the United States healthcare system for the first time.(4) Additionally, there are serious consequences of active tuberculosis during pregnancy,(5) as well as vulnerability to reactivation postpartum.(6–11)

Novel methods to detect latent TB infection are emerging after decades of using only tuberculin skin test.(12) These methods are based on the interferon gamma release assay. According to the 2010 guidelines by the Centers for Disease Control and Prevention (CDC) “An interferon gamma release assay may be used in place of (but not in addition to) a tuberculin skin test in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing M. tuberculosis infection [with special considerations listed by the CDC].” (13) The potential advantages of interferon gamma release assays compared to tuberculin skin test include less cross-reactivity with bacille Calmette-Guérin vaccine, fewer patient visits, and less inter-observer variability in interpretation.(14) On the other hand, interferon gamma release assays are more expensive and require more technical expertise and equipment than tuberculin skin tests.(12) There are currently three interferon gamma release assays approved by the Food and Drug Administration (FDA) for detection of latent TB infection. All require fresh blood to be incubated within a prescribed amount of time, laboratory infrastructure for processing and trained personnel. There is also emerging evidence of an uncertainty zone around the diagnostic cut-off for some interferon gamma release assays that warrants further evaluation.(15, 16). Moreover, few studies have evaluated the use of interferon gamma release assays in normal pregnancy.(17)

Interferon gamma release assays which measure the Th1-mediated immune response may pose a challenge in clinical scenarios, such as pregnancy, in which Th1 immunity is altered. Pregnancy does not appear to alter the performance of the tuberculin skin test. Present and Comstock found that the size of tuberculin skin test induration and incidence of tuberculin skin test conversion or reversion did not differ significantly among 3 groups of women – those who were never pregnant, women who were pregnant at the beginning of the study and then subsequently not pregnant at the end of the study, and women who were not pregnant at the beginning of the study and subsequently became pregnant over the course of the longitudinal study.(19) While the use of interferon gamma release assays may have logistical advantages in the setting of prenatal care, biochemical studies demonstrate that interferon gamma levels are suppressed during pregnancy and, thus, interferon gamma release assay performance may be impaired.(20, 21)

We performed a cross-sectional study to estimate agreement and correlation between the tuberculin skin test and an interferon gamma release assay for detecting latent TB infection in pregnant women.

Materials and Methods

We conducted a cross-sectional study of pregnant women initiating prenatal care at a university-affiliated public hospital between January 5, 2009 and March 15, 2010. Study staff approached women seeking prenatal care at the Women's Health Center at San Francisco General Hospital. Women were eligible if they were at least 16 years of age; pregnancy was confirmed by urine, blood or ultrasound testing; and primary language was English or Spanish. In addition, only women with a negative HIV antibody test during the current pregnancy were eligible for study participation. Exclusion criteria included prior severe reaction to tuberculin skin testing and treatment for latent or active tuberculosis during the current pregnancy.

After obtaining written informed consent, study staff administered a structured questionnaire assessing demographic information, medical history, TB history and risk factors for tuberculosis. Following the questionnaire, participants underwent phlebotomy and then tuberculin skin testing at the University of California San Francisco Clinical and Translational Science Institute Clinical Research Center at San Francisco General Hospital.

Immediately following phlebotomy, trained nurses from the research center placed a tuberculin skin test on all study participants using a standardized protocol. The tuberculin skin test was performed on the volar surface of the forearm according to the Mantoux method using 5 TU of tuberculin (Tubersol).(22) tuberculin skin test results were interpreted 48 to 72 hours after placement and maximum area of induration was measured in millimeters by the research nurses using Sylvac calipers.(23) Using the CDC tuberculin skin test interpretation criteria(24), we defined a positive test if the induration measured 10mm or greater for participants considered recent immigrants (<5 years) from a high-prevalence country (defined by World Health Organization as prevalence greater than 20/100,000 persons),(25) injection drug users, or residents and employees of high-risk congregate settings (homeless shelter, prison, hospitals, or drug rehabilitation unit). For all other study participants, induration of 15 mm or greater was considered positive.

We used the QuantiFERON TB Gold In-Tube (Cellestis ©, Australia) assay, which measures interferon gamma levels in response to presentation of synthetic peptides.(18) According to the manufacturer's specifications, blood was collected into each of the three blood collection tubes, which include a TB antigens (ESAT-6, CFP-10, and TB 7.7) tube, a mitogen (phytohemagglutinin) tube and a negative control tube. Within a maximum of 7 hours of collection, tubes were incubated at 37°C for 16 to 24 hours. Tubes were centrifuged and plasma was collected and frozen at -70°C. ELISA was performed in batches of 28 samples per plate(18) and interpreted according to the manufacturer's protocol. A positive interferon gamma release assay test was defined as greater than or equal to 0.35 IU/ml after accounting for nil control and mitogen control results. A negative interferon gamma release assay test was defined as less than 0.35 IU/ml, after accounting for nil control and mitogen control results. The uncertainty zone was defined as 0.2 IU/ml to 0.5 IU/ml.(15, 16) The uncertainty zone has been documented in other studies of interferon gamma release assays as the range of results around the manufacturer's defined cut-off for which there is a higher likelihood of assay reversion or conversion on repeat testing.

In the enrollment questionnaire, we asked participants if they had received birth bacille Calmette-Guérin vaccination. However, twenty-five percent of patients did not know their birth bacille Calmette-Guérin vaccination status. Therefore, after enrollment was completed, we assigned birth and booster bacille Calmette-Guérin vaccination status to study participants according to the bacille Calmette-Guérin World Atlas.(26) This website, affiliated with McGill University and the Public Health Agency of Canada, allows one to

search for country-specific bacille Calmette-Guérin vaccination policies and practices, including whether birth and/or school-aged booster vaccinations are given, estimated coverage countrywide, and how long the practice has been in place. This information enabled assignment of bacille Calmette-Guérin vaccination based on reported country of birth, birth year and year of immigration to the US.

Sample size was calculated based on an estimated 30% prevalence of positive tuberculin skin test results among pregnant women engaged in prenatal care at San Francisco General Hospital.(27) At an alpha of 0.05 with 90% power to detect kappa of 0.80, we needed 199 patients to participate in the study.

Correlation between tuberculin skin test and interferon gamma release assay was assessed using kappa statistics. Chi-square test was used to compare the frequencies of positive test results among different groups of study recruits. Multivariable logistic regression was used to identify variables independently associated with positive tuberculin skin test and positive interferon gamma release assay results. Multivariable logistic regression was further used to identify variables associated with discordant tuberculin skin test and interferon gamma release assay results. Additional regression analysis was performed to evaluate predictors of women with discordant tuberculin skin test positive and interferon gamma release assay negative results. The correlation between tuberculin skin test and interferon gamma release assay was further explored using assay cut-offs based on the uncertainty zone. All statistical tests were run using STATA (version 11, College Station, TX).

Prior to study initiation, the University of California San Francisco Committee on Human Research approved the protocol. All study participants provided written, informed consent.

Results

Overall, 220 participants were enrolled with 21 women (9.5%) lost to follow-up between enrollment and tuberculin skin test reading at 48–72 hours. One hundred ninety-nine women were included in the final analysis. Of these 199 study participants, over 70% were in their first trimester of pregnancy. The median age was 25 years. The majority had a high school education (58%) and was of Hispanic ethnicity (70%). (See Table 1) Over 65% of participants were born in a country with high tuberculosis prevalence defined as greater than 20/100,000 persons.(25)

Twenty-three percent of study participants had a positive tuberculin skin test compared to 14% who had a positive interferon gamma release assay result. There was 77.39% agreement between the tests with a kappa of 0.26. (Table 2) Agreement and correlation using either lower or upper bound uncertainty zone cut-offs for interferon gamma release assay or excluding results within the uncertainty zone were not different from the primary analysis.

There were 12 participants with interferon gamma release assay results in the uncertainty zone. (Table 3) Over half of these women had a negative tuberculin skin test, but there was a wide range of skin test induration (0–17.96 mm). Fifty percent of these women with interferon gamma release assay results in the uncertainty zone would have been vaccinated at birth with bacille Calmette-Guérin according to bacille Calmette-Guérin World Atlas and were born in a country with a high prevalence of TB. Thirty percent of women reported receiving the bacille Calmette-Guérin vaccine (data not shown).

In unadjusted analysis, Hispanic ethnicity, Black race and birth bacille Calmette-Guérin vaccination were associated with a positive tuberculin skin test. However, in multivariable analysis adjusting for Hispanic ethnicity, Black race and birth bacille Calmette-Guérin

vaccination, birth bacille Calmette-Guérin vaccination was significantly associated with positive tuberculin skin test (OR 4.33, 95% CI 1.40–13.48) (Table 4). In unadjusted analysis, Hispanic ethnicity and birth bacille Calmette-Guérin vaccination were both associated with a positive interferon gamma release assay result. However in logistic regression, no variable was significantly associated with interferon gamma release assay positivity. (Table 4)

Of the 45 women with discordant tuberculin skin test and interferon gamma release assay results, 32 women (71.1%) were tuberculin skin test positive and interferon gamma release assay negative. Nearly 70% of these 32 women had received tuberculin skin test screening prior to this index pregnancy. Over 80% of women with tuberculin skin test positive and interferon gamma release assay negative results had birth bacille Calmette-Guérin vaccination and 87.5% of these women were born in a country with a high prevalence of tuberculosis. In univariate analysis, predictors of tuberculin skin test positive and interferon gamma release assay negative results included being born in a country with a high prevalence of TB (OR 4.46, $p=0.01$) and birth bacille Calmette-Guérin vaccination (OR 3.12, $p=0.02$). (Table 5) On the other hand, Black race was associated with a lower odds of being tuberculin skin test positive and interferon gamma release assay negative compared to other races (OR 0.12, $p<0.05$). In multivariable analysis, adjusting for race, previous tuberculin skin test screening, and birth in high prevalence country, birth in high prevalence country was marginally associated with tuberculin skin test positive and interferon gamma release assay negative results (OR 2.94, 95% CI 0.86–9.97, $p=0.08$).

Discussion

In our study, we sought to estimate the agreement and correlation between tuberculin skin test and interferon gamma release assay for detection of latent TB infection in an ethnically-diverse population of pregnant women. Overall agreement between the two screening methods was 77.39%, with poor correlation (kappa 0.26), and we were unable to identify statistically significant predictors of discordant results. However, when we analyzed the risk factors associated with positive results for each of the tests separately, we found that birth bacille Calmette-Guérin vaccination was an independent predictor of tuberculin skin test positivity. In contrast, birth bacille Calmette-Guérin vaccination was not associated with interferon gamma release assay positivity. The agreement and correlation between tuberculin skin test and interferon gamma release assay in our study was lower than that described in studies of other populations with altered immunity, including HIV-infected and transplant patients, and intact immunity, such as Spanish healthcare workers.(23, 28–30) However, assay agreement and correlation found in our study is similar to or better than those found among Navy recruits, Indian healthcare workers, and Dutch TB contacts.(31–33) In the only other study we know of that compared tuberculin skin test and interferon gamma release assay results in healthy pregnant women, Chehab et al found 91% agreement between tuberculin skin test and interferon gamma release assay among pregnant women in Kansas.(17) However, the prevalence of tuberculin skin test or interferon gamma release assay positivity was very low in this study population (less than 10% of positive tuberculin skin test and less than 5% of positive interferon gamma release assay), which may explain the higher agreement between the two tests. (34)

We did not observe interferon gamma release assay with indeterminate results. Indeterminate results are rare events (2–4% of tests) that cannot be interpreted and, when they arise, the sample must be retested for a definitive result. Indeterminate results may be due to a technical problem in the laboratory or failure of positive controls to stimulate interferon gamma production(12). Indeterminate results have been reported in subjects infected with HIV (23, 35), as well as non-Chinese Asian adults.(36) We may not have seen

indeterminate results because the effect of pregnancy on the immunologic response is not as severe as observed among individuals infected with HIV, and because just 8% of our population was Asian.

Interestingly, we did have 12 women with interferon gamma release assay values in the gray zone. However, altering the cut-off value defining a positive interferon gamma release assay did not change our results. Because the emerging literature suggests that interferon gamma release assays are prone to conversions and reversions in serial testing (15, 16, 37) we assessed for risk factors associated with discordant results but did not find any associations.

The main limitation of this study is the lack of gold standard to define which of the two methods is better to diagnose latent TB infection. Moreover, given that the rate of tuberculin skin test positivity was lower than we had anticipated based on prior studies in our pregnant population, we may have lacked power to identify predictors of discordant tuberculin skin test positive and interferon gamma release assay negative results. Lastly, the results from this study may be specific to the QuantiFERON TB Gold In-Tube and not generalizable to all the interferon gamma release assays currently available.

Taken together, the clinical significance of tuberculin skin test positive and interferon gamma release assay negative results remains unknown and could represent a false positive tuberculin skin test or false negative interferon gamma release assay results. We found that birth bacille Calmette-Guérin vaccination was associated with tuberculin skin test positivity but not interferon gamma release assay positivity. This may be indirect evidence that birth bacille Calmette-Guérin vaccination is associated with a persistently positive tuberculin skin test beyond the previously described 5–10 years. Data suggest that 20–25% of those receiving school-age bacille Calmette-Guérin boosters will have a persistently positive tuberculin skin test at least 10 years later.(38) On the other hand, many studies have found that a single bacille Calmette-Guérin vaccination received during infancy does not appear to have a lasting impact on tuberculin skin test results.(39) While tuberculin skin test positivity diminishes over the years after vaccination, the rate cannot be accurately measured due to different types of bacille Calmette-Guérin strains administered and subject genetic variability.(22) Given the increased specificity of antigens tested, interferon gamma release assays likely overcome this limitation of the tuberculin skin test cross reactivity with bacille Calmette-Guérin. On the other hand, tuberculin skin test positive and interferon gamma release assay negative results may occur because interferon gamma release assay performance is impaired in pregnancy. We did not find an association between gestational age and interferon gamma release assay positivity or discordant results, suggesting that pregnancy may not alter the performance of interferon gamma release assays. Nonetheless, the shift from Th1 to Th2 predominance occurs very early in pregnancy and therefore these immune changes may have had a systematic impact on interferon gamma release assay performance in our study.(6, 21) Our study highlights that in pregnancy the relationship between bacille Calmette-Guérin vaccination and discordant tuberculin skin test and interferon gamma release assay results is not clear. Future studies could estimate interferon gamma release assay specificity by performing the assay in healthy, very low risk pregnant women and estimating assay sensitivity by performing the assay among pregnant women with known active TB, though assay performance may differ for the diagnosis of latent versus active TB. Ideally, longitudinal studies in women before, during and after pregnancy would evaluate the impact of pregnancy on the performance of interferon gamma release assay, including its association with values in the gray zone. In summary, this study of an urban population of pregnant women found poor agreement and correlation between tuberculin skin test and interferon gamma release assay in detecting latent TB infection. While we found no statistically significant predictors of discordant results between these screening tests, there was a trend toward birth in high prevalence country as a predictor of

tuberculin skin test positive and interferon gamma release assay negative discordance. While some have argued in favor of only using interferon gamma release assay to detect latent TB infection because of its apparent increased specificity compared to tuberculin skin test,(40, 41) an ideal screening test optimizes sensitivity.(42) As long as elimination of TB remains a goal in the United States, it is critical to optimize our screening methods for latent TB infection among high-risk populations, including immigrant pregnant women who may be accessing healthcare in the United States for the first time. Given that much is still unknown about the performance of interferon gamma release assays in pregnancy, we would argue that further research is necessary before tuberculin skin test is abandoned for screening of latent TB infection in pregnancy.

Acknowledgments

Presented at three oral presentations: May 11, 2010- San Francisco Gynecologic Society Resident Research Symposium, San Francisco, California; May 19, 2010- UCSF CTSI Resident Research Symposium, San Francisco, California; and the August 5, 2010- Infectious Diseases Society for Obstetrics and Gynecology Annual Meeting, Sante Fe, New Mexico.

Supported by the Mount Zion Health Fund of the Jewish Community Endowment Grant, the UCSF Clinical Translational/Science Institute Resident Research Fund, Cellectis Ltd., Carnegie, Australia (in kind donation of test kits), and NIH/NCRR UCSF-CTSI grant number UL1 RR024131.

Literature Cited

1. Prevention CFDCa. MMWR Morbidity and Mortality Weekly Report. 2009. Decrease in reported tuberculosis cases- United States, 2009; p. 289-96.
2. Pratt R, Robinson V, Navin T. Trends in Tuberculosis- United States, 2008. MMWR. 2009; 58(10): 249–55. [PubMed: 19300406]
3. American Thoracic Society/Centers for Disease C, Prevention/Infectious Disease Society of A. . Controlling Tuberculosis in the United States. Am J Respir Crit Care Med. 2005; 172(9):1169–227. [PubMed: 16249321]
4. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep. 2000; 49(RR-6):1–51.
5. Efferen LS. Tuberculosis in Pregnancy. Curr Opin Pulm Med. 2007; 13(3):205–11. [PubMed: 17414128]
6. Singh N, Perfect J. Immune Reconstitution Syndrome and Exacerbation of Infections in Pregnancy. Clin Infect Dis. 2007; 45(9):1192–9. [PubMed: 17918082]
7. Brar HS, Golde SH, Egan JE. Tuberculosis Presenting as Puerperal Fever. Obstet Gynecol. 1987; 70(3PT 2):488–90. [PubMed: 3627610]
8. Cheng VC, Woo PC, Lau SK, et al. Peripartum Tuberculosis as a Form of Immunorestitution Disease. Eur J Clin Microbial Infect Dis. 2003; 22(5):313–7.
9. Brandstetter RD, Murray HW, Mellow E. Tuberculosis Meningitis in a Puerperal Woman. JAMA. 1980; 244(21):2440. [PubMed: 6776303]
10. Covelli HD, Wilson RT. Immunologic and Medical Considerations on Tuberculin-sensitized Pregnant Patients. Am J Obstet Gynecol. 1978; 132(3):256–9. [PubMed: 707564]
11. Wilson EA, Thelin TJ, Dilts PV Jr. Tuberculosis Complicated by Pregnancy. Am J Obstet Gynecol. 1973; 115(4):526–4. [PubMed: 4685503]
12. Schluger NW, Burzynski J. Recent advances in testing for latent TB. Chest. 2010; 138(6):1456–63. [PubMed: 21138881]
13. Centers for Disease C, Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis infection- United States 2010. MMWR. 2010; 59(RR 5):1–13.
14. Nahid P, Pai M, Hopewell PC. Advances in diagnosis and treatment of tuberculosis. Proc Am Thorac Soc. 2006; 3(1):103–10. [PubMed: 16493157]

15. Pai M, Joshi R, Dogra S, Zwerling AA, Gajalakshmi D, Goswami K, et al. T-cell assay conversions and reversions among household contacts of tuberculosis patients in rural India. *Int J Tuberc Lung Dis.* 2009; 13(1):84–92. [PubMed: 19105884]
16. van Zyl-Smit RN, Zwerling A, Dheda K, Pai M. Within-subject variability of interferon-g assay results for tuberculosis and boosting effect of tuberculin skin testing: a systematic review. *PLoS one.* 2009; 4(12):e8517. [PubMed: 20041113]
17. Chehab BM, Kallail KJ, El Fakih RO, Zackula RE, Minns GO. Use of the QuantiFERON-TB Gold Assay in Pregnant Patients. *Kansas Journal of Medicine.* 2010; 3(2):24–30.
18. Cellestis. QuantiFERON-TB Gold (In-Tube Method): Package Insert. 2007.
19. Present PA, Comstock GW. Tuberculin sensitivity in pregnancy. *Am Rev Respir Dis.* 1975; 112(3):413–6. [PubMed: 1172402]
20. Shi Y, Fau-Ling B, Ling B, Fau-Zhou Y, Zhou Y, Fau-Gao T, et al. Interferon-gamma expression in natural killer cells and natural killer T cells is suppressed in early pregnancy. *Cell Mol Immunol.* 2007 Oct; 4(5):389–94. (1672–7681 (Print)). [PubMed: 17976320]
21. Kruse N, Fau-Greif M, Greif M, Fau-Moriabadi NF, Moriabadi NF, Fau-Marx L, et al. Variations in cytokine mRNA expression during normal human pregnancy. *Clin Exp Immunol.* 2000 Feb; 119(2):317–22. (0009-9104 (Print); 0009-9104 (Linking)). [PubMed: 10632669]
22. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. *Am J Respir Crit Care Med.* 2000; 161(4 Pt 1):1376–95. [PubMed: 10764337]
23. Luetkemeyer AF, Charlebois ED, Flores LL, Bangsberg DR, Deeks SG, Martin JN, et al. Comparison of an Interferon- γ Release Assay with Tuberculin Skin Testing in HIV-infected Individuals. *American Journal of Respiratory and Critical Care Medicine.* 2007; 175(7):737–42. [PubMed: 17218620]
24. Centers for Disease C. Tuberculosis (TB) Fact Sheets Tuberculin Skin Testing.
25. WHO. WHO Global Health atlas- allows looking up countries TB stats. 2009. Global Health Atlas.
26. Zwerling, AB.; Verma, Marcel; Brewer, Aman; Menzies, Timothy; Pai, Dick; Madhukar. BCG World Atlas: A Database of Global BCG Vaccination Policy and Practice.
27. Cruz CA, Caughey AB, Jasmer R. Postpartum Follow-Up of a Positive Purified Derivative (PPD) Among an Indigent Population. *Am J Obstet Gynecol.* 2005; 192(5):1455–7. [PubMed: 15902136]
28. Manuel O, Humar A, Preiksaitis J, Doucette K, Shokoples S, Peleg AY, et al. Comparison of quantiferon-TB gold with tuberculin skin test for detecting latent tuberculosis infection prior to liver transplantation. *Am J Transplant.* 2007; 7(12):2797–801. [PubMed: 17941955]
29. Alvarez-Leon EE, Espinosa-Vega E, Santana-Rodriguez E, Molina-Cabrillana JM, Perez-Arellano JL, Caminero JA, et al. Screening for tuberculosis infection in spanish healthcare workers: Comparison of the QuantiFERON-TB gold in-tube test with the tuberculin skin test. *Infection control and hospital epidemiology: the official journal of the Society of Hospital Epidemiologists of America.* 2009; 30(9):876–83. [PubMed: 19614541]
30. Bartalesi FV, Goletti S, Fiorelli D, Fiori C, Melchiorre G, Tortolie DEM, Benucci A, Girardi M, Cerinic E, Bartoloni MMA. QuantiFERON-TB Gold and the TST are both useful for latent tuberculosis infection screening in autoimmune diseases. *Eur Respir J.* 2009; 33:586–93. [PubMed: 19047313]
31. Kang YA, Lee HW, Yoon HI, et al. 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.* 2005; 292(22):2756–61. [PubMed: 15941805]
32. Mazurek GH, Zajdowicz MJ, Hankinson AL, Costigan DJ, Toney SR, Rothel JS, et al. Detection of Mycobacterium tuberculosis infection in United States Navy recruits using the tuberculin skin test or whole-blood interferon-gamma release assays. *Clin Infect Dis.* 2007; 45(7):826–36. [PubMed: 17806046]
33. Arend SM, Thijsen SFT, Leyten EMS, Bouwman JJM, Franken WPJ, Koster BFPJ, et al. Comparison of Two Interferon-gamma Assays and Tuberculin Skin Test for Tracing Tuberculosis

- Contacts. American Journal of Respiratory and Critical Care Medicine. 2007; 175(6):618–27. [PubMed: 17170386]
34. Hoehler FK. Bias and prevalence effects on kappa viewed in terms of sensitivity and specificity. J Clin Epidemiol. 2000; 53(5):499–503. [PubMed: 10812322]
35. Jonnalagadda S, Lohman Payne B, Brown E, Wamalwa D, Maleche Obimbo E, Majiwa M, et al. Latent tuberculosis detection by interferon gamma release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1-infected women and their children. J Infect Dis. 2010; 202(12):1826–35. [PubMed: 21067370]
36. Lee JY, Choi HJ, Park IN, Hong SB, Oh YM, Lim CM, et al. Comparison of two commercial interferon-gamma assays for diagnosing Mycobacterium tuberculosis infection. Eur Respir J. 2006; 28(1):24–30. [PubMed: 16611658]
37. Pai M, Joshi R, Dogra S, Mendiratta DK, Narang P, Kalantri S, et al. Serial Testing of Health Care Workers for Tuberculosis Using Interferon- γ Assay. American Journal of Respiratory and Critical Care Medicine. 2006; 174(3):349–55. [PubMed: 16690977]
38. Menzies R, Vissandjee B. Effect of bacille Calmette-Guerin vaccination on tuberculin reactivity. Am Rev Respir Dis. 1992; 145(3):621–5. [PubMed: 1546843]
39. Menzies D. What does tuberculin reactivity after bacille Calmette-Guerin vaccination tell us? Clin Infect Dis. 2000; 31 (Suppl 3):S71–4. [PubMed: 11010826]
40. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Annals of Internal Medicine. 2007; 146(5):340–54. [PubMed: 17339619]
41. Pai M, Riley LW, Colford JM Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. Lancet Infect Dis. 2004; 4(12):761–76. [PubMed: 15567126]
42. Deeks JJ. Systematic reviews in health care: Systematic reviews of evaluations of diagnostic and screening tests. BMJ. 2001; 323(7305):157–62. [PubMed: 11463691]

Table 1

Demographics and Risk Factors for Tuberculosis Among Pregnant Women Screened for Latent Tuberculosis Infection (n=199)

Demographics	
Median Age (years) [range]	25 (17–41)
Education n, (%)	
None	6 (3.02)
Less than 8 years	31 (15.57)
High School	116 (58.29)
College	42 (21.11)
Graduate Degree	4 (2.01)
Race/Ethnicity n, (%) [*]	
White	17 (8.54)
Hispanic	139 (69.85)
American Indian	2 (1.01)
Black	36 (18.09)
Asian	16 (8.04)
Gestational age at Enrollment	
Median in weeks (Range)	10 (5–39)
Trimester at Enrollment n, (%)	
1 st trimester (≤12 weeks)	141 (70.85)
2 nd trimester (12–24 weeks)	44 (22.11)
3 rd trimester (≥ 25 weeks)	14 (7.04)
Risk Factors for TB Infection n (%)	
TB History	
Previous TST screening n, (%)	
Yes	123 (61.81)
No	70 (35.18)
Don't know	6 (3.02)
Previous positive TST n, (%) [†]	
Yes	9 (7.32)
No	112 (91.05)
Don't know	2 (1.63)
Birth BCG Vaccination n, (%) [‡]	
Yes	123 (61.81)
No	76 (38.19)
Booster BCG Vaccination n, (%) [‡]	
Yes	62 (31.16)
No	137 (68.84)

Demographics	
Lived or worked in homeless shelter, prison, hospital or drug rehabilitation unit	
Yes	30 (15.15)
No	168 (84.85)
Birth in country with high TB prevalence [§]	
Yes	130 (65.33)
No	69 (34.67)

TB, tuberculosis; TST, tuberculin skin test; BCG, bacille Calmette-Guérin.

* Column total greater than 100% because participants were able to check more than one race category

[†] Totals of 123 persons had prior TST testing

[‡] According to bcgatlas.org(26)

[§] Countries defined by World Health Organization as prevalence greater than 20/100,000 persons(25)

Table 2

Correlation between Interferon Gamma Release Assay test and Tuberculin Skin Test by Differential Interferon Gamma Release Assay Cut-Offs

Standard Cut-Off 0.35 IU/ml			
	TST Positive n, (%)	TST Negative n, (%)	Total
IGRA Positive	14, (30.43)	13, (8.5)	27
IGRA Negative	32, (69.57)	140, (91.5)	172
Total	46, (100)	153, (100)	
Agreement 77.39%, Kappa 0.26 (95% CI 0.12, 0.40)			
Cut-Off Excluding values 0.2–0.5 IU/ml (uncertainty zone)			
			Total
IGRA Positive	13, (30.95)	10, (6.9)	23
IGRA Negative	29, (69.05)	135, (93.1)	164
Total	42, (100)	145, (100)	
Agreement 79.1%, Kappa 0.29 (95% CI 0.15, 0.43)			
Cut-Off 0.2 IU/ml (lower limit of uncertainty zone)			
			Total
IGRA Positive	17, (36.96)	18, (11.76)	35
IGRA Negative	29, (63.04)	135, (88.24)	164
Total	46, (100)	153, (100)	
Agreement 76.38%, Kappa 0.27 (95% CI 0.13, 0.41)			
Cut-Off 0.5 IU/ml (upper limit of uncertainty zone)			
			Total
IGRA Positive	13, (71.74)	10, (6.54)	23
IGRA Negative	33, (28.26)	143, (93.46)	176
Total	46, (100)	153, (100)	
Agreement 78.39%, Kappa 0.26 (95% CI 0.12, 0.40)			

TST, tuberculin skin test; IGRA, Interferon gamma release assay; SE, standard error.

Table 3

Select Characteristics of Participants With Interferon Gamma Release Assay Results in the Uncertainty Zone*
(n=12)

	n (%)
Positive TST Result	4 (38.46)
Median TST Induration (mm) [range]	0 (0–17.96)
Birth BCG Vaccination [†]	6 (50)
Booster BCG Vaccination	5 (41.67)
Birth in country with high TB prevalence [‡]	6 (50)
Trimester at Enrollment	
First	10 (83.33)
Second	2 (16.67)
Third	0 (0)

TST, tuberculin skin test; BCG, bacille Calmette-Guérin; TB, tuberculosis.

* Uncertainty zone as defined by Pai, et al²⁵, as interferon gamma release assay values between 0.2–0.5 IU/ml

[†] According to bcgatlaz.org(26)

[‡] Countries defined by World Health Organization as prevalence greater than 20/100,000 persons(25)

Table 4

Predictors of Screen Test Positivity (n=193)*

Predictors of Tuberculin Skin Test Positive				
	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Hispanic ethnicity	2.44(1.06–5.62)	0.04	0.58 (0.19–1.73)	0.32
Black race	0.07 (0.01–0.56)	0.01	0.14 (0.02–1.37)	0.09
Previous TST screening	0.96 (0.48–1.91)	0.91	1.29 (0.63–2.68)	0.49
Birth BCG vaccination	5.62(2.25–14.04)	0.00	4.33 (1.40–13.48)	0.01
Predictors of Interferon Gamma Release Assay Positive				
Hispanic ethnicity	3.97 (1.15–13.72)	0.03	3.00 (0.38–20.35)	0.12
Black race	0.52(0.15–1.85)	0.32	3.81 (0.38–23.78)	0.30
Previous TST screening	1.16 (0.49–2.75)	0.73	1.55 (0.63–3.79)	0.34
Birth BCG vaccination	3.09(1.12–8.56)	0.03	3.12 (0.67–14.52)	0.15

TST, tuberculin skin test; OR, odds ratio; BCG, bacille Calmette-Guérin.

* Six missing values for previous TST screen

Table 5

Predictors of Tuberculin Skin Test-Positive and Interferon Gamma Release Assay-Negative Results (n=193)*

Variable	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P
Black race	0.12 (0.02–0.92)	0.04 [†]	0.23 (0.02–2.17)	0.20
Previous TST screening	1.30 (0.58–2.95)	0.52	1.72 (0.75–3.96)	0.20
Birth in country with high TB prevalence	4.46 (1.50–13.31)	0.01 [†]	2.94 (0.86–9.97)	0.08

OR, odds ratio; TST, tuberculin skin test; TB, tuberculosis.

* Six missing values for previous TST screen

[†] p<0.05, statistically significant