# Screening for Latent Tuberculosis in Pregnant Women:
# A Comparison of an Interferon-γ Release Assay with Tuberculin Skin Testing in Pune, India

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## ABSTRACT

Background: Active tuberculosis (TB) during pregnancy has poor outcomes for mother and child. Women in resource-limited countries are not routinely screened for latent TB infection (LTBI). LTBI screening has relied on the tuberculin skin test (TST), which is operator-dependent, requires a return visit, and lacks sufficient sensitivity and specificity. A commercially available interferon-gamma release assay, QuantiFERON® Gold Test-in-tube (QGIT), is more sensitive and specific for LTBI screening in the general population of low endemic countries. Its performance in high endemic countries and among pregnant women, however, is not well established.

Methods: We conducted a cross-sectional study of 152 HIV-negative women seeking prenatal care at a public government hospital in Pune, India from January-September 2011. Trained counselors and nurses administered questionnaires that included sociodemographic, medical, and TB symptom history. Women with negative TB symptom screens received TST and QGIT testing. Agreement was measured using the kappa statistic, and percent positivity with binomial exact confidence intervals was estimated.

Results: The median gestational age was 27 weeks (IQR: 23-30). Of the 152 women enrolled, 140 had their TST read and 18% were positive (95% CI 12%-25%). Twelve (8%) did not return for TST reading. Thirty-three percent were QGIT positive (95% CI 26%-42%) and 2% had indeterminate results. There was 74% agreement between the two tests (kappa= 0.4). Among the 31 discordant results, 26 had positive QGIT and negative TST while 5 had a positive TST and negative QGIT

Conclusions: The prevalence of LTBI was 16% if defined as having both a positive TST and QGIT but varied widely if looking at the results of either test individually. Overall, TST and QGIT had fair to moderate concordance. Loss to follow-up remained a challenge for the TST. Women with discordant results were more likely to have a positive QGIT and negative TST, while other studies report a higher proportion of people with positive TSTs and negative QGITs. Longitudinal follow-up of this group will help determine which test has a higher predictive value during pregnancy in high endemic countries.

## INTRODUCTION

Three-hundred-thousand Indians die of TB every year, with women of reproductive age suffering disproportionately. The immune changes of pregnancy increase the risk of reactivating latent TB infection but also mask the symptoms of active TB disease until after delivery.

Latent TB screening is not routinely done in many high endemic settings because of the flaws of the tuberculin skin test (TST), which include:
1) Low sensitivity and specificity
2) Requirement of the patient to return in 48-72 hrs for interpretation
3) Operator variability in placement and interpretation
4) Cross reaction in those receiving the BCG vaccine

The Interferon-γ release assays (IGRAs) do not have the same limitations, but their performance in pregnant women is not well established.

## METHODS

*Study Population*
- HIV-negative pregnant women seeking prenatal care during their third trimester

*Study Site*
- Antenatal clinic at an urban, public government hospital in Pune, India

*Screening*
- Sociodemographic questionnaire administered by trained counselors
- Medical and obstetric history questionnaire administered by trained nurses
- Active TB symptom screen by trained nurses
- TST and QuantiFERON® Gold Test-in-tube testing by trained nurses and lab staff, respectively

*Analysis*
- Agreement was measured using the kappa statistic
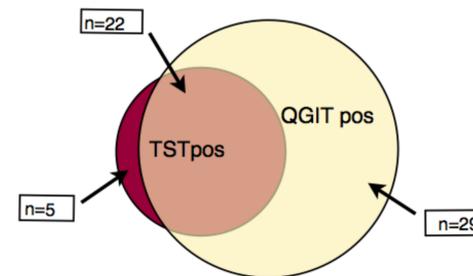- Percent positivity with binomial exact confidence intervals was estimated

This study was approved by the IRBs at Johns Hopkins School of Medicine, Weill Cornell Medical College and BJ Medical College (in Pune).

## RESULTS

**Table 1. Sociodemographic and Clinical characteristics: Total and by concordance status**

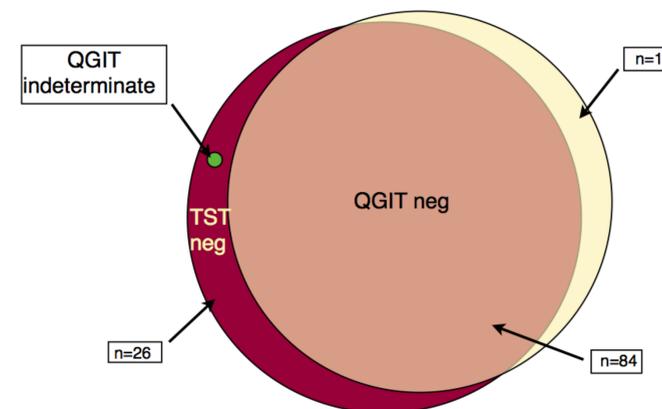| Characteristic | Total N=152 (%) | Concordant N=106 (%) | Discordant (QGIT+/TST-) N=25 (%) |
|---|---|---|---|
| Gestational age in weeks, median (IQR) | 27 (23-30) | 27 (23-30) | 27 (23-28) |
| Urban/ Peri-urban residence | 146 (96%) | 101 (94%) | 25 (100%) |
| Number of people living in household | | | |
| Adults (median, range) | 5 (2-11) | 4 (2-10) | 5 (2-11) |
| Children (median, range) | 1 (0-10) | 1 (0-8) | 1 (0-5) |
| Two or less rooms in the house | 123 (81%) | 86 (80%) | 19 (76%) |
| Housewife | 140 (92%) | 98 (92%) | 24 (96%) |
| Less than 4th grade education | 18 (12%) | 14 (13%) | 2 (8%) |
| Smoker in the house | 30 (20%) | 23 (21.5%) | 3 (12%) |
| Went to bed hungry because of no food | 12 (7.9%) | 11 (10%) | 1 (4%) |
| Chest infections in the past year | 1 (0.7%) | 0 (0%) | 1 (4%) |
| History of TB treatment | 1 (0.7%) | 0 (0%) | 1 (4%) |
| Household or close contact with TB | 5 (3.3%) | 2 (1.8%) | 2 (8%) |
| Contact with MDR-TB | 3 (2%) | 1 (0.9%) | 2 (8%) |
| Household member with HIV | 1 (0.7%) | 0 (0%) | 0 (0%) |

**Table 2. Mean TST Induration and IFN-γ concentrations in concordant vs discordant**

| Test Result | Mean TST Induration (mm, range) | Mean IFN-γ Concentration (IU/mL, range) |
|---|---|---|
| TST+/QGIT+ | 16 (10-25) | 4.6 (0.46- >10) |
| TST+/ QGIT- | 12.6 (10-17) | 0.18 (0.08-0.27) |
| TST-/QGIT+ | 1 (0-5) | 2.9 (0.59-8.79) |
| TST-/QGIT- | 0.75 (0-5) | 0.13 (0-0.35) |

**Figure 1a. Concordance of positive TSTs with positive QGIT tests**



n=22
n=5
n=29
TSTpos
QGIT pos

TST pos= 27    QGIT pos = 51

**Figure 1b. Concordance of negative TSTs with negative QGIT tests**



QGIT indeterminate
n=14
n=26
n=84
TST neg
QGIT neg

QGIT indet=3    TST neg= 113    QGIT neg= 98

## RESULTS CONT'D

Of the 140 women that returned for TST reading, 27 (18%) were positive (95% CI 12%-25%). Fifty-one (34%) of the total 152 women were QGIT positive (95% CI 26%-42%). Twelve (8%) did not return for TST reading. Three (2%) had indeterminate QGIT results.

There was 74% agreement between the two tests (kappa=0.4). Twenty-two (16%) women had both a positive TST and QGIT. Thirty-one (22%) had discordant results. Five (3.5%) were TST positive/QGIT negative and 26 (18.5%) were TST negative/QGIT positive.

Of the 12 women who did not return for TST reading, 3 (25%) of them were QGIT positive and 9 (75%) were QGIT negative. All of the women with indeterminate QGIT results had a negative TST.

One woman had a history of TB in the past and she had a negative TST and positive QGIT. Of the five women with a history of contact with someone diagnosed with TB, two of them had a positive QGIT and three of them had a negative QGIT. Four of them returned for TST reading and were all negative. The one who did not return had a negative QGIT.

## CONCLUSIONS

➤ TST and QGIT displayed fair-to-moderate agreement in HIV-negative pregnant women in a high TB endemic area.

➤ If defined as having both TST and QGIT positive, the prevalence of latent TB infection was 16%, less than half of the Indian national rate.

➤ Loss to follow-up remained a challenge for the TST results with 18% not returning for interpretation of results.

➤ Most women with discordant results had a positive QGIT and a negative TST. Longitudinal follow-up will help determine the significance of this.

➤ Ongoing data collection from the HIV negative and positive cohorts will address the impact of stage of pregnancy and HIV infection on test results.

## ACKNOWLEDGEMENTS