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# Comparison of QuantiFERON-TB gold in tube test versus tuberculin skin test for screening of latent tuberculosis infection in Saudi Arabia: A population-based study

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**Abstract:**

**OBJECTIVES:** To compare QuantiFERON-TB gold in tube (QFT-GIT) test with tuberculin skin test (TST) in detecting latent tuberculosis infection (LTBI) among a general population in Saudi Arabia.

**METHODS:** A population-based cross-sectional study was conducted between July 2010 and March 2013 among individuals randomly selected from the list of those receiving care at primary healthcare centers in three provinces of Saudi Arabia; Central, Western, and Eastern provinces. Those younger than 5 years, immunocompromised, had a current or previous history of active TB, LTBI, or who were receiving anti-TB medications were excluded. Informed consent was obtained before the study questionnaire was completed. Participants were then evaluated for LTBI using QFT-GIT test followed immediately by TST.

**RESULTS:** Of the 1369 subjects included in the final analysis, QFT-GIT was positive in 124 (9.1%) and TST was positive in 127 (9.3%). Positive concordance was observed in 49 (3.6%) subjects while negative concordance was observed in 1167 (85.2%) subjects. The overall agreement between the two tests was 88.8% with a significant kappa ( $\kappa$ ) test ( $\kappa = 0.332$ ,  $P < 0.001$ ). Concordance was significantly higher in younger age, female gender, single status, students, primary education, living in middle-sized families, and never smoked.

**CONCLUSIONS:** The overall agreement of TST and QFT-GIT for the detection of LTBI among a Saudi general population was 88.8%. QFT-GIT is probably comparable to TST for detecting LTBI in an intermediate TB burden country with high at birth bacille Calmette Guérin vaccination coverage. Further prospective studies are needed to compare the ability of both tests to predict TB disease.

**Key words:**

Latent mycobacterium tuberculosis infection, QuantiFERON-TB gold in tube test, Saudi Arabia, tuberculin skin test

Approximately, one-third of the world's population is infected with *Mycobacterium tuberculosis* as estimated by the World Health Organization.<sup>[1]</sup> While early identification and treatment of latent tuberculosis infection (LTBI) may limit further dissemination of TB, this still remains a challenge. Diagnosis of LTBI has been dependent on the tuberculin skin test (TST) for many years, and a quick and reliable alternative is needed.<sup>[2]</sup> Placing and reading the TST requires experience and a second patient visit 48–72 h after placement to determine the reading. This has made the TST a difficult and challenging diagnostic tool for identifying LTBI cases.<sup>[3]</sup> QuantiFERON-TB gold in tube (QFT-GIT), on the other hand, has been developed using TB-specific antigens performed on a single blood sample.<sup>[4,5]</sup> As of 2005, QFT-GIT has been recommended for diagnosing LTBI by the United States Centers for Disease Control and Prevention.<sup>[6]</sup> While

other countries, such as UK, Canada, Spain, and Italy, have recommended a two-step approach where the TST is followed by QFT-GIT.<sup>[7,8]</sup> In Saudi Arabia, TST continues to be preferred for

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diagnosing LTBI. Concerns for adopting QFT-GIT in Saudi Arabia do exist because of the relative lack of comparative population-based studies between QFT-GIT and TST in Saudi Arabia or from similar countries with moderate TB endemicity and a high bacille Calmette Guérin (BCG) coverage rate at birth.

The objective of the current study was to compare the performance of QFT-GIT to TST in identifying LTBI among a general Saudi population.

## Methods

### Study setting

The study was conducted at primary healthcare centers (PHC) of the Ministry of National Guard-Health Affairs in three provinces of Saudi Arabia. The Ministry of National Guard-Health Affairs serves a population over 1 million through, five main hospitals and over thirty PHCs are available in the three provinces. Primary health care centers in Riyadh, Jeddah, and Al-Ahsa were chosen as province representative primary study sites for patient enrollment.

### Design

A population-based cross sectional study was conducted between July 2010 and March 2013. Required ethical approvals were obtained from King Abdullah International Medical Research Center.

### Study population

The study was done among the population served by PHCs of the Ministry of National Guard-Health Affairs. Inclusion criteria included Saudi nationalities who had been residing in the country and were available to participate in the study. Exclusion criteria included age <5-year-old (to exclude the BCG vaccination effect on the results of the study as it is given routinely at birth for all newborn in Saudi Arabia), current or previous history of TB disease, current or previous history of exposure to anti-TB medications, immunocompromised persons including leukemia, lymphoma, other cancer under chemotherapy, hemodialysis, organ transplantation, chronic steroid or immunosuppressive therapy, or HIV.

### Randomization and recruitment

Subjects were randomly chosen from the lists of medical record numbers of served population in the chosen PHCs. Chosen subjects were contacted by the study coordinator. Study aim, design, and tests were explained to potential adult participants or to one of the parents of potential child participants. Participants were booked for clinical visits for evaluation, responding to the questionnaire testing after signing the informed consent. Participants were then evaluated for LTBI using QFT-GIT test followed immediately by TST.

### Tuberculin skin test and blood sample collection for QuantiFERON-TB gold in tube

During the initial clinic visit, 0.1 ml of purified protein derivative test using five unit ampoules (Sanofi Pasteur limited, Toronto, Ontario, Canada) was injected intradermally into the volar aspect of the subject's forearm. The transverse induration diameter was measured no sooner than 48 h and no later than 72 h by a trained nurse. In addition, during the initial visit, 3 ml blood sample was collected from the subject by venipuncture

for the QFT-GIT assay. All information on the patients were coded and available only to the principal investigator, the research coordinator, and the statistician.

### Statistical analysis

All categorical variables were presented as frequencies and percentages while continuous variables were presented as means and standard deviations or median and interquartile range, as appropriate. Agreement between the results of the TST and QFT-GIT tests was assessed by using kappa ( $\kappa$ ) coefficients. To detect the association of sociodemographic characteristics of the study participants with the concordance of the results of TST and QFT-GIT tests, Chi-square or Fisher's exact test, as appropriate, were used for categorical variables. All  $P$  values were two-tailed. A  $P < 0.05$  was considered as significant. SPSS software (release 16.0, SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

## Results

A total 1443 out of 1745 (82.7%) subjects responded and accepted to participate in the study [Table 1]. A total of 74 out of 1443 subjects (5%) were excluded from the study due to different reasons: Unavailability of QFT-GIT test results due to poor handling and or transportation of the blood sample ( $n = 38$ ), indeterminate results of QFT-GIT test ( $n = 27$ ), unavailability of TST readings due to "clinic no show" within 72 h ( $n = 5$ ), and age <5 years ( $n = 4$ ). Data of the remaining 1369 subjects were included in the final analysis. A total 763 (55.7%), 313 (22.9%), and 293 (21.4%) subjects were from the Central, Eastern, and Western Provinces, respectively. Of those, 597 (43.6%) were male and the mean age of participants was 26.3 years. More than half of the studied population was single 782 (57.6%). Other demographic details are included in Table 1.

LTBI test was positive by TST in 127 (9.3%) subjects and by QFT-GIT in 124 (9.1%) subjects. Only 49 (3.6%) subjects were positive for both tests whereas 202 (14.8%) were positive by either test [Figure 1]. Comparing the results of the QFT-GIT with those of the TST, both tests had a significant overall agreement of 88.8% ( $[1167 + 49]/[1369]$ ;  $\kappa = 0.332$ ; 95% confidence interval = 0.23–0.43;  $P < 0.001$ ). The LTBI prevalence index was 0.82 and prevalence-adjusted kappa was 0.78 ( $P < 0.001$ ). Negative concordance comprised 85.2% of the results, and positive concordance comprised 3.6%. However, positive TST but negative QFT-GIT comprised 5.7% of the results, and negative TST but positive QFT-GIT comprised 5.5% [Table 2].

Concordance between TST and QFT-GIT tests among all study participants was 88.8%. This proportion was significantly higher among those of younger age 5–14 years (96.3%,  $P < 0.001$ ), female gender (91.3%,  $P < 0.05$ ), unmarried subjects (93.2%,  $P < 0.001$ ), primary school education (94.5%,  $P < 0.001$ ), students (94.4%,  $P < 0.001$ ), those living in Western province (91.8%,  $P < 0.001$ ), and living in middle-sized (6–10) families (90.3%,  $P = 0.038$ ), never smoked cigarette (89.8%,  $P < 0.001$ ), and never smoked shisha (89.6%,  $P = 0.001$ ). On the other hand, family income was not significantly associated with concordance ( $P = 0.169$ ) [Table 3].

**Table 1: Sociodemographic characteristics of 1369 study participants enrolled to compare tuberculin skin test with QuantiFERON TB gold in tube in Saudi Arabia**

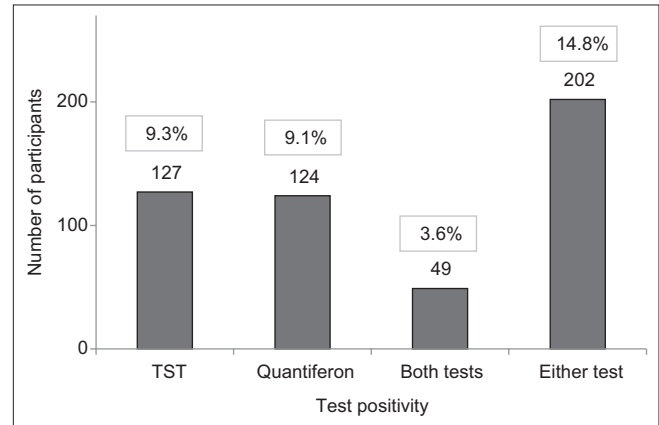
Characteristics	Value* (%)
Age (years)	
Mean±SD	26.3±19.0
5-14	591 (43.2)
15-44	502 (36.7)
45-64	204 (14.9)
≥65	72 (5.3)
Gender	
Male	597 (43.6)
Female	772 (56.4)
Marital status	
Single	782 (57.6)
Married	543 (40.0)
Divorced/widowed	33 (2.4)
Education	
Illiterate	175 (13.2)
Primary school	559 (42.3)
Mid/high school	455 (34.4)
University and above	134 (10.1)
Occupation	
Military	183 (15.3)
Civilian	67 (5.6)
Housewife	161 (13.4)
Student	691 (57.6)
Unemployed	53 (4.4)
Retired	45 (3.8)
Family income	
Median and IQR	8,000 (5,500-10,000)
≤6000	178 (33.6)
6001-9000	194 (36.6)
>9000	158 (29.8)
Family size	
Median and IQR	8 (6-10)
≤5	261 (22.0)
6-10	691 (58.2)
>10	235 (19.8)
Geographic provinces	
Central province	763 (55.7)
Eastern province	313 (22.9)
Western province	293 (21.4)
Cigarette smoking	
Never	1220 (90.0)
Current	87 (6.4)
Previous	49 (3.6)
Pack-years of smoking (median and IQR)	10 (5-20)
Hookah (shisha) smoking	
Never	1282 (94.8)
Current	38 (2.8)
Previous	32 (2.4)
Serving-years of smoking (median and IQR)	15 (5-30)

\*Number (percentage) unless mentioned otherwise. SD = Standard deviation, IQR = Interquartile range

**Table 2: Agreement between the results of tuberculin skin test and QuantiFERON TB Gold in tube among 1369 study participants enrolled in Saudi Arabia**

	TST		Total
	Negative (<10 mm)	Positive (≥ 10 mm)	
QFT-GIT			
Negative	1167	78	1245
Positive	75	49	124
Total	1242	127	1369

$\kappa=0.332$ ,  $P<0.001$ , adjusted  $\kappa=0.78$ ,  $P<0.001$ , agreement=concordant pairs=(1167+49)/(1369)=88.8%, disagreement=nonconcordant pairs=(78+75)/(1369)=11.2%. QFT-GIT = QuantiFERON TB Gold in tube, TST = Tuberculin skin test



**Figure 1: Results of tuberculin skin test and QuantiFERON-TB Gold in tube among 1369 study participants in Saudi Arabia**

## Discussion

In comparing QFT-GIT to TST in detecting LTBI, in a general population in Saudi Arabia, we found an agreement of 88.8% for both positive and negative concordance. Worldwide studies show a fair to good concordance from 65.4% to 92.5% among healthcare workers,<sup>[9-12]</sup> while others reported a much lower concordance rate among health care workers (HCWs).<sup>[13,14]</sup> Other studies showed total agreement of 82% among army personnel,<sup>[15]</sup> 64.4% among lupus patients,<sup>[16]</sup> 78.6% among hematopoietic stem cell patients,<sup>[17]</sup> 85.1% among liver transplant candidates,<sup>[18]</sup> 89.3% among HIV patients,<sup>[19]</sup> and 65% among hemodialysis patients.<sup>[20]</sup> In Saudi Arabia, almost all studies were among particular groups of patients or HCWs. While no studies were conducted in Saudi Arabia evaluating the agreement between the two tests among general population, a recent study among HCWs showed 73.7% overall agreement between the two tests ( $\kappa = 0.33$ ,  $P < 0.01$ ) with 60.1% negative concordance and 13.5% positive concordance.<sup>[21]</sup> Another recent study done on dialysis, patients showed 75.5% overall agreement between the two tests ( $\kappa = 0.34$ ).<sup>[22]</sup> A third study reported overall agreement of TST and T spot QFT test OF 90.9% ( $\kappa = 0.46$ ) among kidney donors.<sup>[23]</sup> However, the sample size of these studies was small, and the results may not be representative of a larger population.

**Table 3: Concordance between tuberculin skin test and QuantiFERON TB Gold in tube by sociodemographic characteristics among 1369 study participants in Saudi Arabia**

	Concordant (%)	Discordant (%)	P
Overall	1216 (88.8)	153 (11.2)	-
Age (years)			
5-14	569 (96.3)	22 (3.7)	<0.001
15-44	425 (84.7)	77 (15.3)	
45-64	168 (82.4)	36 (17.6)	
≥65	54 (75.0)	18 (25.0)	
Gender			
Male	511 (85.6)	86 (14.4)	0.001
Female	705 (91.3)	67 (8.7)	
Marital status			
Single	729 (93.2)	53 (6.8)	<0.001
Married	448 (82.5)	95 (17.5)	
Divorced/widowed	29 (87.9)	4 (12.1)	
Education			
Illiterate	147 (84.0)	28 (16.0)	<0.001
Primary school	528 (94.5)	31 (5.5)	
Mid/high school	391 (85.9)	64 (14.1)	
University and above	109 (81.3)	25 (18.7)	
Occupation			
Military	149 (81.4)	34 (18.6)	<0.001
Civilian	53 (79.1)	14 (20.9)	
Housewife	141 (87.6)	20 (12.4)	
Student	652 (94.4)	39 (5.6)	
Unemployed	44 (83.0)	9 (17.0)	
Retired	32 (71.1)	13 (28.9)	
Family income			
≤6000	148 (83.1)	30 (16.9)	0.169
6001-9000	158 (81.4)	36 (18.6)	
>9000	140 (88.6)	18 (11.4)	
Family size			
≤5	229 (87.7)	32 (12.3)	0.038
6-10	624 (90.3)	67 (9.7)	
>10	198 (84.3)	37 (15.7)	
Geographic province			
Central province	690 (90.4)	73 (9.6)	<0.001
Eastern province	257 (82.1)	56 (17.9)	
Western province	269 (91.8)	24 (8.2)	
Cigarette smoking			
Never	1096 (89.8)	124 (10.2)	<0.001
Current	73 (83.9)	14 (16.1)	
Previous	35 (71.4)	14 (28.6)	
Hookah (shisha) smoking			
Never	1149 (89.6)	133 (10.4)	0.001
Current	31 (81.6)	7 (18.4)	
Previous	22 (68.8)	10 (31.2)	

In the current study, unadjusted kappa testing the agreement of the results of QTF-G and TST tests (considering positive TST at ≥10 ml induration size) was 0.33, which is considered fair agreement. However, we believe that the agreement in the studied population is considerably reduced by the relatively low prevalence of the disease (as indicated by a high prevalence index of 0.82). Therefore, when adjusting for the prevalence,

adjusted kappa became 0.78, which is considered substantial agreement.

Despite the overall agreement of 88.8% for both positive and negative concordance, it is of concern that both tests being positive were in only 3.6% (49/1369) subjects whereas either test being positive was 14.8% (202/1369). The understanding that either test conducted alone for screening the population for LTBI will miss 5.5%, (75/1369) and 5.7%, (78/1368) for TST and QFT-GIT, respectively, is of concern. While screening a general population is rarely conducted outside national studies to identify prevalence rates, the shortcomings of using either test alone is a reasonable argument for conducting both tests simultaneously. In fact, guidelines from other countries such as the UK, Spain, Italy, and Canada have provided special scenarios in which a two-step testing is applied. For example, in the Canadian guidelines, both tests are preferred when the risk of infection or the likelihood of progression to TB disease is high.<sup>[18,24]</sup> The UK and European guidelines, on the other hand, highlight the need to use both tests, specifically in patients with HIV and a low CD4 count or any other condition leading to significant immunocompromise.<sup>[25-27]</sup> In all guidelines, however, it is clear that neither the TST nor the QFT-GIT should be used for the diagnosis of active TB disease for any age group.

In Saudi Arabia, as in many countries around the world, the BCG vaccine is administered at birth. However, it was found that the BCG vaccine may produce a temporary positive TST result that declines with age.<sup>[28-30]</sup> The timing between the vaccination and TST leading to such false positive TST result has not been clearly determined. For that reason, we excluded in our study children below the age of 5 years. On the hand, while the QFT-GIT test is not expected to be affected by the BCG vaccine, there is no clear data on the efficacy of the GFT-GIT tests for diagnosing LTBI in children. To date, using either test for diagnosing LTBI should be according to national guidelines, if available, and expert opinion.

The major strength of our study is the stratified random sampling technique used in recruitment, the large number of study subjects, and the inclusion of three geographic provinces in Saudi Arabia. Our limitations are that we did not plan to follow individuals with a positive TST or QFT-GIT for the development of TB disease and the fact that we excluded children below the age of 5 years. Both limitations will be addressed in a future study.

## Conclusions

The overall agreement of TST and QFT-GIT for the detection of LTBI among a Saudi general population was 88.8%. QFT-GIT is probably comparable to TST for detecting LTBI in an intermediate TB burden country with high at birth bacille calmette guerin vaccination coverage. Further prospective studies are needed to compare the ability of both tests to predict TB disease.

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### Conflicts of interest

There are no conflicts of interest.

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