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# Comparison of Quantiferon-TB Gold In-Tube Assay and Tuberculin Skin Testing for the Screening of Latent Tuberculosis among Household Contacts of MDR-TB in Malaysia

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**Abstract:** Tuberculin skin test (TST) has long been the gold standard of latent tuberculosis infection (LTBI) screening among active TB and LTBI cases. However, as this test has well-known limitations, interferon-gamma (IFN)–ý release assays (IGRAs) are currently acknowledged as the best commercially available method for screening active TB and LTBI. This study aimed to determine the agreement between the TST and the Quanti FERON-TB Gold In-Tube assay (QFT-GIT) for detecting LTBI among household contacts index cases in Malaysia. A cross-sectional study was conducted among household contacts of MDR-TB index cases that attended three respiratory specialist clinics as well as those who were admitted at multi-center hospitals in Peninsular Malaysia. Blood samples were collected in QFT-GIT Gold In-Tubes and test was performed by enzyme-linked immunosorbent assay. QFT-GIT Gold In-Tube analysis software was used to calculate the results. Kappa statistical analysis was used to analyze the obtained data. Seventy household contacts of index cases including 38 (54.3%) females and 32 (45.7%) males with a mean age (SD) of 36.12 (16.88) years were enrolled in this study. LTBIs among household contacts with positive and negative TSTs were 12 (70.6%; >10 mm) and 5 (29.4%; =10 mm) respectively. QFT-GIT positive and negative cases were 9 (32.1%) and 19 (67.9%) respectively. Most of the LTBI cases had previously received BCG vaccination (31, 79.5%). The clinical agreement between TST and QFT-GIT was relatively poor ($\kappa = 0.28$). It can be concluded that comparison of TST and QFT-GIT results in household contacts showed relatively poor concordance.This study highlights the importance of contact tracing using a new method for LTBI detection in high-risk groups.

**Key words:** Household Contacts · Index Case · LTBI · TST · QFT-GIT · Malaysia

## INTRODUCTION

Tuberculosis (TB) is the second most frequent cause of death by an infectious agent[1] and its diagnosis depends on the trio of susceptibility to infection, availability of diagnostic tools and the status of the disease (hat is whether active or latent infection). A suspected TB is confirmed by at least one of three elements; a sputum smear positive for Acid Fast Bacilli (AFB), strong clinical evidence and chest x-ray suggesting TB. However, each of these elements is relatively non-specific [2].

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The tuberculin skin test (TST) has long been the gold standard for screening latent tuberculosis infection (LTBI) but is known to have several limitations such as delayed T-cell type hypersensitivity, cross-reactivity with a wide range of environmental *mycobacteria* and BCG vaccine. It also has high false-positive and false-negative rates [3]. QuantiFERON-TB Gold In-Tube Assay (QFT-GIT) is a new screening tool for LTBI and TB surveillance [4, 5]. The QFT-TB Gold In-Tube assay (Cellestis Limited, Carnegie, Victoria, Australia) and T-SPOT.TB assay (Oxford Immunotec, Oxford, UK) are two types commercially available and has been approved by the U.S. Food and Drug Administration.

Interferon-gamma (IFN)–ý release assays (IGRAs) are blood tests that detect *Mycobacterium tuberculosis* infection. These tests are based on the interferon-gamma released from sensitized T lymphocytes in whole blood incubated for 18–24 h with purified protein derivative (PPD) from specific *M. tuberculosis* and antigens. These antigens include overlapping peptides of early secreted antigenic target 6 (ESAT-6), culture filtrate protein 10 (CFP-10) and a portion of tuberculosis antigen TB7.7 (Rv2654). The test is conducted by enzyme-linked immunosorbent assay (ELISA) and results are calculated using QFT-TB software analysis [4, 6].

Kwakernaak *et al*. [7] reported several advantages of IGRAs. First, IGRAs are highly specific and therefore, unaffected by prior BCG vaccination. Second, since IGRAs can be repeated without boosting, a baseline two-step testing protocol is unnecessary. Third, the testing protocol requires only one visit to a hospital. Previous studies suggest that IGRAs using ESAT-6/CFP-10 antigens are more specific and sensitive than TST for diagnosing LTBI. Therefore, IGRAs are increasingly recommended for LTBI detection. The WHO has recently published recommendations on the use of IGRAs in low- and medium-income countries to detect LTBI. Published studies stated that IGRAs potentially provide more specific and accurate estimates of annual risks of LTBI infection [4-7]. Close contacts of multi-drug resistance tuberculosis (MDR-TB) cases, such as household members, family and friends, are most likely to become infected. Considering their intense or prolonged exposure to index cases, such contacts are highly advised to undergo testing [8]. LTBI treatment is very important, especially in recently infected household contacts to prevent progression to active disease. Efficient tools for LTBI diagnostics are thus extremely important; such tools are also considered vital components of an effective TB control program.

However, data describing the agreement between the performance of QFT-GIT and that of conventional TST for LTBI diagnosis in household contacts of index cases are limited. Therefore, this study aimed to determine the agreement between the TST and QFT-GIT by detecting LTBI among household contacts of index cases in Malaysia

## MATERIALS AND METHODS

**Study Design:** A cross-sectional study was conducted among household contacts of index cases warded at six hospitals as well as those who attended three respiratory specialist chest clinics from five states [Kelantan, Perak, Pulau Pinang, Johor Bahru and The Federal Territories (Kuala Lumpur)] in peninsular Malaysia. Study recruitment was conducted from May 2012 to April 2013. Samples were collected from household contacts of index cases. All index cases were confirmed by proven sputum smear cultures positive for MDR-TB based on laboratory tests according to the WHO protocol for drug susceptibility testing (DST) and the Ministry of Health, Malaysia.

**Household Contact:** The degree of household contact is defined as family or friends living in the same house, sleeping on the same bed, staying in the same room, or usually sharing meals with index cases. MDR-TB was defined as a strain of *M. tuberculosis* resistant to at least two of the most effective first-line drugs (Isoniazid and rifampicin). DST confirmed that all cases presented with either MDR-TB or XDR-TB by positive culture and drug sensitivity testing [9].

Household contacts of the index cases were identified through the medical records of index cases and interviews. All household contacts, including family and friends who lived in the same house with the index cases, were included in the study. Unrelated household contacts such as visiting persons and/or those who did not stay in the same house as the index cases were excluded from the study. Household contacts that had other medical conditions or serious illnesses that may affect the result of the study (QFT-GIT) were excluded from the study. Participation was based on voluntary willingness to enroll in the study. The study was verbally explained to all household contacts and written informed consent was obtained prior to the study. In the case of children, verbal assent and parental consent were obtained.

All available household contacts were asked to provide blood samples for the LTBI test. All important demographic characteristics were collected from adults and children living as household contacts. All the participants were asked information such as socio-demographic characteristics, BCG vaccination and history of previous TB.

**Sample Collections and Procedures:** TST was done by trained health care workers according to International guidelines [10]. Results were read after 72 hours of injection. All the household contact were traced and asked to come to the nearest health care center or hospitals and home visit was done for participants who did not return for TST reading.

For the TST, a test dose (0.1ml) of 5 tuberculin units of purified protein derivative (PPD) solution was intradermally injected into the volar aspect of the forearm with a 26–27 gauge needle by trained professionals from the aforementioned respiratory chest clinics and hospitals. The results were interpreted and the induration diameter of the raised, blanched weal (not the erythema) was read after 48–72 h. Positive and negative TSTs had induration diameters of =10 and <10 mm respectively.

Trained professionals collected 1 $cm^3$ of peripheral blood from all household contacts. The samples were collected using three different QFT-GIT, which include TB antigen (ESAT-6, CFP-0 and TB 7.7) tube, mitogen (phytohemagglutinin) tube and a negative control tube. The contents of each tube were mixed by shaking the tubes vigorously for 5 seconds or 20 times to ensure that the entire inner surface of the tube was coated with blood. This procedure was carried out within a maximum of 6 hours after blood collection. All ~~of~~ the samples were immediately brought to the nearest serology laboratory for purpose of storage. The entire test was performed in serology laboratory in other study centers and also department of medical microbiology and parasitology HUSM. The samples were incubated at 37 °C for 16–24 hours and then centrifuged. The plasma was collected and frozen at -70 °C. ELISA was performed in batches of 28 samples per plate and interpreted according to the manufacturer's protocol.

**Ethical Consideration:** Ethical issues were considered in the entire participant's and data retrieved from medical records. Ethical approval was obtained from the Human Research and Ethics Committee of Universiti Sains Malaysia [Ref. No. USMKK/PPP/JE PeM/243.3 (4.1)] and the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR No. 12-90-10809). The confidentiality and privacy of information were ensured.

**Statistical Analysis:** Statistical Package for Social Sciences (SPSS) version 20.0 was used for data entry and analysis. All of the data were double-checked for accuracy of variables and detection of missing or erroneous entries.The descriptive analysis was presented as mean and SD for numerical variables and the data were presented as frequency (*n*) and percentage (%) for categorical variables. Kappa analysis to confirm clinical agreement was applied.

## RESULTS

The current study was designed to determine the agreement between QFT-GIT and TST. A total of 70 household contacts were enrolled in this study and their demographic characteristics are presented in Table 1. Kappa analysis was only performed in 45 cases; 25 cases were missing from the TST group. The TST group was traced by trained professionals from a multi-center hospital in Malaysia. According to MOH guidelines for TB programs, LTBI was traced and investigated in all index cases of newly diagnosed TB.

Table 1 shows the demographic characteristics of the household contacts. A total of 78 household subjects were contacted and invited to participate in this study, but only 70 invitees participated. Eight household contacts refused to provide blood samples and were thus withdrawn from the study. A total of 38 (54.3%) females and 32 (45.7%) males with mean (SD) age of 36.12 (16.88) years old were included in this study. The highest educational attainment of the participants was secondary school [12 (38.7%) and 17 (43.6%)] and ~~[~~11 (35.5%) and 14 (35.9%)~~]~~ were unemployed. The majority of the LTBI cases had no previous diagnosis of TB; 24 (77.2%) and 38 (97.4%) cases were negative and positive, respectively, for LTBI. Most of the LTBI cases had previously received BCG vaccination 21 (67.7) and 31 (79.5%).

**Clinical Agreement Between the Two Tests:** Table 2 presents the clinical agreement between QFT-GIT and TST. The kappa agreement between two tests was relatively poor ($k = 0.28$ and $P = 0.084$). LTBIs among the household contacts of MDR-TB index cases with positive and negative TSTs numbered 5 (29.4%; =10 mm) and 12 (70.6%; =10 mm), respectively. Moreover, QFT-GIT-negative and -positive cases numbered 9(32.1%) and 19 (67.9%), respectively.

Table 1: Demographic characteristics of household contacts index cases (n= 70)

| Variables | QFT-GIT Negative for LTBI *n* (%) | QFT-GIT Positive for LTBI *n* (%) | *P* value |
|---|---|---|---|
| Age* | 36.12 ± 16.88 | | |
| Gender | | | |
| Female | 15 (48.4) | 23 (59.0) | 0.377[a] |
| Male | 16 (51.6) | 16 (41.0) | |
| Race | | | |
| Indian | 2 (6.5) | 4 (10.3) | 0.913 [b] |
| Chinese | 3 (9.7) | 5 (12.8) | |
| Foreign | 13 (41.9) | 15 (38.5) | |
| Malay | 13 (41.9) | 15 (38.5) | |
| Marital Status | | | |
| Single | 8 (25.8) | 14 (35.9) | 0.266 [a] |
| Married | 23 (74.2) | 25 (64.1) | |
| Educational level | | | |
| No formal education | 3 (9.7) | 6 (15.4) | 0.715 [b] |
| Primary | 8 (25.8) | 10 (25.6) | |
| Secondary | 12 (38.7) | 17 (43.6) | |
| Diploma | 6 (19.4) | 3 (7.7) | |
| Degree and above | 2 (6.5) | 2 (5.1) | |
| Occupational level | | | |
| Government employee | 2 (6.5) | 1 (2.6) | 0.930 [b] |
| Private employee | 9 (29.0) | 14 (35.9) | |
| Self-employed | 4 (12.9) | 4 (10.3) | |
| Housewife | 5 (16.1) | 6 (15.4) | |
| Unemployed | 11 (35.5) | 14 (35.9) | |
| Previous history of TB | | | |
| Yes | 21 (67.7) | 1 (2.6) | 0.009 [a] |
| No | 10 (32.3) | 38 (97.4) | |
| BCG scar present | | | |
| Yes | 21 (67.7) | 31 (79.5) | 0.264[a] |
| No | 10 (32.3) | 8 (20.5) | |

TB, *tuberculosis*; TST, tuberculin skin test; BCG, Bacille Calmette Guérin; QFT-GIT, QuantiFERON-TB Gold in Tube Assay

[a]P value for chi-square test

[b]P value for Fisher exact test

* Mean and Standard deviation (SD)

Table 2: Correlation between QuantiFERON-TB Gold in Tube test and tuberculin skin test by kappa analysis (*n*=45)

| Clinical agreement | QFT-GIT Negative | QFT-GIT Positive | Total | *P value* |
|---|---|---|---|---|
| Negative TST | 5 (29.4%) | 9 (32.1%) | 14 (31.4%) | 0.084 |
| Positive TST | 12 (70.6%) | 19 (67.9%) | 31 (68.9%) | |
| Total | | | 45 (100.0%) | |
| Kappa | | | 0.28 | |

Clinical agreement and correlation between TST and QFT-GIT [$k = 0.28$ ($P < 0.0848$)].

## DISCUSSION

Several studies [11-17] have reported that IGRAs are the best and newest detection method with high specificity and sensitivity for detecting *M. tuberculosis* infection among active TB or LTBI cases and household contacts. We compared the QFT-GIT test with the TST and an investigation was carried out to determine their agreement. We further sought to determine whether or not QFT-GIT can replace TST.

For several decades, TST was the only test available for LTBI detection. TST has been proven to be useful in clinical practice, but the method presents several disadvantages attributed to its low sensitivity and specificity (particularly from significant cross-reactivity to BCG) and numerous operational drawbacks [17-19]. QuentiFERON-TB Gold In-Tube assay and T-SPOT.TB assay are included in the United Kingdom Guidelines [18]. The guidelines recommend a two-stage strategy of TST testing followed by IGRAs to confirm a positive TST result. The WHO recently recommended the use of IGRAs in medium- and low-income countries to detect LTBI. Although previous studies have examined the agreement between the two tests as well as the effects of active TB treatment on QFT-GITresponses, the results obtained in these studies are inconsistent with those reported in this paper [18, 19]. The WHO currently recommends LTBI treatment of HIV-infected patients in developing countries and acceptable tool for LTBI diagnosis is crucial to achieve TB elimination [20].

The results of this present study demonstrated poor agreement between TST and QFT-GIT ($k = 0.28$). QFT-GIT had higher positive detection rates [19 (61.3%)] than TST [9 (32.1%)]. The test, however, was unable to identify statistically significant predictors of discordant results. Undetermined results were excluded from the kappa analysis in both groups. The poor agreement between the two tests may be attributed to a number of reasons. The small sample size may affect the result of the tests. Undetermined results were observed in QFT-GIT samples and these results were attributed to technical errors, sample incubation errors and laboratory failure. False positive rate of the TST in non-progressive subjects was observed in this study subject for an independent predictor of TST positive.

Reactive TSTs may be attributed to remote or non-*Mycobacterium* infections that can give false-positive TST results with indurations of 5-14 mm [21]. Prior BCG vaccination may explain a false-positive TST. Lower QTB-GIT sensitivity during TB infection detection is also

possible. In this study, the majority of the participants had previously received BCG vaccination. The results of the two tests showed several inconsistencies. Similar findings have been reported by studies carried out in Melbourne, Australia and Taiwan [22,23]. The inconsistencies observed may be due to BCG vaccination, which may result in false-positives and false-negatives for TST.

Given that both TST and QFT-GIT measure the presence of *M. tuberculosis*; our results could be interpreted as follows. Absence of mycobacterial infection: 14 subjects in our study were not infected; both TST and QFT-GIT results were negative. Possible mycobacterial infection: a positive TST result with a negative QFT-GIT reaction may be attributed to previous exposure to NTM or history of BCG vaccination for which an organism closely related to the tubercular bacillus, *M. bovis*, is used as an antigen. Either factor could have led to a false-positive reaction. A negative TST but positive QFT-GIT may indicate that the subject has TB infection, but the TST is false-negative. This result may occur during immunosuppression or natural waning of immunity or as a result of NTM, such as *M. kansasii*, *M. marinum*, or *M. szulgai*, on IGRAs [22]. High probability of infection: both tests indicated the presence of *M. tuberculosis*. Thus, the subjects with positive results in both tests require close follow-up in order to prevent progression to active TB.

According to the findings of this study, QFT-GIT detected more positive cases than TST, but the agreement between these two tests were relatively poor ($k$ = 0.28). Positive reactions may be associated with prior BCG vaccination. The present study is better than those found in Navy recruits, Indian and Dutch TB contacts [14]. Our results are similar to those in other studies performed in USA and Germany ($k$ = 0.37 and 0.26, respectively) and positive reactions had poor agreement between TST and QFT-GIT were also associated with prior BCG vaccination [24-25].

Studies conducted in Italy reported good agreement between the two tests ($\kappa$ = 0. 58 and $\kappa$ = 1.0, respectively) [26]. The difference in results could be due to several reasons, such as the high rate of TB infection, poor economic status and the high number of unvaccinated BCG individuals. Other studies found good agreement between the two tests, particularly among unvaccinated individuals ($\hat{e}$ = 0.58) and in countries with low rates of TB infection unvaccinated populations [27].

A study in India reported 100% agreement ($\kappa$ = 1.0) between TST and QTB-GIT in BCG scar-negative children compared with 94% ($\kappa$ = 0.63) in scar-positive children. BCG vaccination did not significantly affect either the TST or QFT-TB results [28]. Several reasons, including the higher rate of TB infection in India, the lower rate of HIV infection in the Malaysian population compared with the Indian population and the better economic status of Malaysians compared with Indians, may explain the differences in results. However, this test has showed an acceptable diagnostic test for determining recent *M. tuberculosis* infection in a vaccinated population in Malaysia. Similar results were found in at least four other studies [29-30].

The United States Center for Disease Control recommends a 6-9 month LTBI regimen with INH for high-risk subjects, such as those with HIV infection or organ transplant recipients with positive QFT-GIT or TST results [31]. However, the German Central Committee against TB assay (QFT or T-SPOT.TB) before offering LTBI treatment [32]. In this study, no treatment was given to any of the participants because the investigation focused on close contacts of MDR-TB patients and second-line drugs are generally more toxic than first-line medications.

## CONCLUSION

The clinical agreement between TST and QFT-GIT was relatively poor. Both TST and QFT-GIT can be used to detect TB disease or LTBI. Considering that the tests do not measure the same components of the immunological response, they are not interchangeable. Both tests should be used in conjunction with risk assessment, radiography and other medical and diagnostic evaluations. The QFT-GIT test can be especially useful and more specific than TST in detecting LTBI in countries such as Malaysia, which has high BCG vaccination coverage. Screening and treatment of household contacts of active cases of pulmonary *M. tuberculosis* are important. Further research is necessary to improve the accuracy of QFT-GIT. More risk assessments considering both individual characteristics and intensity of exposure should also be conducted within household contacts. Relevant authorities should continuously strive toward improving preventive and control measures to reduce the risk of *M. tuberculosis* transmission among household contacts.

**Conflict of Interest:** The authors have declared that there is no potential conflict of interest.

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