Performance of QuantiFERON-TB Gold In-Tube test and Tuberculin Skin Test for diagnosis of latent tuberculosis infection in BCG vaccinated health care workers

Cenk Babayigit
Burcin Ozer
Tacettin Inandi
Cahit Ozer
Nizami Duran
Orhan Gocmen

Background: Tuberculin skin test (TST) has been used for years as an aid in diagnosing latent tuberculosis infection (LTBI) but it suffers from a number of well-documented performance and logistic problems. Quantiferon-TB Gold In Tube test (QFT-GIT) has been reported to have better sensitivity and specificity than TST. In this study, it was aimed to compare the performance of a commercial IFN-γ-release assay (QFT-GIT) with TST in the diagnosis of HCWs at risk for latent TB infection in BCG vaccinated population.

Material/Methods: Hundred healthy volunteer health care workers were enrolled. All were subjected to TST and QFT-GIT. Results were compared among Health Care Workers (HCWs) groups in terms of profession, workplace, working duration.

Results: TST is affected by previous BCG vaccinations and number of cases with QFT-GIT positivity is increased in accordance with the TST induration diameter range. QFT-GIT result was negative in 17 of 32 TST positive (≥15 mm) cases and positive in 4 of 61 cases whose TST diameters are between 6–14 mm, that is attributable to previous BCG vaccination(s). It was negative in all cases with TST diameters between 0–5 mm. HCWs with positive QFT-GIT results were significantly older than the ones with negative results. Furthermore duration of work was significantly longer in QFT-GIT positive than in negative HCWs.

Conclusions: There was a moderate concordance between QFT-GIT and TST, when TST result was defined as positive with a ≥15 mm diameter of induration. We suggest that QFT-GIT can be used as an alternative to TST for detection of LTBI, especially in groups with high risk of LTBI and in population with routine BCG vaccination program.

MeSH Keywords: Skin Tests • Quantifieron-TB Gold In-Tube • Latent Tuberculosis • Tuberculin Test
Background

World Health Organization declared tuberculosis (TB) a global public health emergency in 1993. One third of the world’s population, approximately 2 billion people, are thought to be latently infected with Mycobacterium tuberculosis (M. tuberculosis) and globally, 9 million people develop active disease attributable to M. tuberculosis infection annually [1]. Although subjects with latent M. tuberculosis infection (LTBI) do not manifest overt symptoms of active tuberculosis and are not infectious, they are at increased risk for developing active disease and becoming infectious [1]. Health Care Workers (HCW) are at risk of exposure to patients with undetected active tuberculosis in the hospital setting, so they are at increased risk for M. tuberculosis infection [1–4]. The risk for M. tuberculosis infection among HCW was reported to be 3.2 times higher than normal population [5].

The diagnosis and treatment of latent tuberculosis (TB) infection has a critical role in the control of TB [6]. Tuberculin skin test (TST) has been most commonly used for the diagnosis of latent tuberculosis until the beginning of this century. The tuberculin test is based on a delayed-type hypersensitivity reaction that occurs in those infected with mycobacterial extracts termed purified protein derivatives [7]. Although the TST is widely used for diagnosing LTBI, it has some limitations. It’s reported that its sensitivity may be decreased due to some factors like malnutrition, severe tuberculosis diseases and immunodeficiency. In addition, the biggest disadvantage of TST is the cross-reaction with nontuberculous mycobacteria or with Mycobacterium bovis vaccine strains [8,9]. It has been reported that the skin test may lead to false positive results in the vaccinated and infected patients with nontuberculous mycobacteria.

Recently, IFN-γ release assays such as the QuantiFERON-TB Gold In-Tube (QFT-GIT) containing Mycobacterium tuberculosis-specific antigens have been reported to be a more specific and sensitive tool for the determination of Mycobacterium tuberculosis [10]. These newly developed tests measure the production of interferon-gamma released from sensitized lymphocytes after stimulated with specific TB antigens [11].

In literature, IFN-γ release assays have been shown to have high sensitivity and specificity [8,12]. The QFT-GIT has been compared with the TST in the general population including children, health-care workers, and immunocompromised patients in many studies [13–18]. However, there is rather limited research in literature that evaluates their performance for the diagnosis of latent TB infection in vaccinated HCWs. Also, few studies have compared both tests (TST and QFT-GIT) in vaccinated HCWs. Previous studies have shown that the results of these two test contain many contradictions on issues such as TST and QFT-GIT the positivity rates and consistency ratios of TST and QFT-GIT [19–24].

In this study, it was aimed to compare the performance of the QuantiFERON-TB Gold In-Tube (QFT-GIT) with TST in the diagnosis of HCWs at risk for latent TB infection in BCG vaccinated population.

Material and Methods

Study population

Volunteer health care workers from Mustafa Kemal University Hospital (Antakya, Turkey), Antakya State Hospital and Antakya Tuberculosis Control Dispensary were enrolled in this study. After providing written informed consent, all volunteers completed a detailed questionnaire about place and duration of employment as a health care staff, number of BCG vaccinations, presence of any symptom or medical history of TB disease, factors predisposing to TB disease such as any immune-deficiency state or diabetes mellitus, presence or medical history of anti-TB or any immune suppressive treatment. Volunteers with the predisposing factors to TB, history of TB or anti-TB treatment, recently performed TST or known positive TST result, or history of any immune suppressive treatment were not included.

Eventually, a total of 100 healthy volunteer participants were composed of 36 doctors, 34 nurses, 18 microbiology laboratory stuff and 12 paramedic personals (from anaesthesiology, radiology, and emergency departments). The doctors and the nurses were stuff of different clinics such as chest diseases, internal medicine, infectious diseases where TB patients were followed up.

QFT-GIT assay

The test was processed at our microbiology department of our hospital’s central laboratory in accordance with the manufacturer’s recommendations. With QFT-GIT, whole blood is drawn into 3 precoated tubes (2 control tubes and 1 TB antigen tube). One of the controls has nil antigen which serves as negative control; the other has a mitogen protein, which serves as positive control. The TB antigen tube contains 3 peptides specific to M. tuberculosis: ESAT-6, CFP-10 and TB7.7. After incubation of the blood with antigens for 16–24 hours, the amount of IFN-γ released is determined by subtracting the amount in the nil from the amount in the ESAT-6 -, CFP-10 -, TB7.7 -, or mitogen stimulated plasma. The QFT-GIT test result is considered “positive” if the IFN-γ response level is at least 0.35 IU/ml over the nil concentration. Nil concentrations
of at least 8.0 IU/ml and mitogen differences of less than 0.5 IU/ml were considered “indeterminate” on the basis of manufacturer’s guidelines. Volunteers with indeterminate QFT-GIT results were excluded from the study population, because the test could not be repeated since test kit had deployed. All QFT-GIT test positive subjects underwent further clinical investigation with symptom query, chest x-ray (and if needed sputum stain for Mycobacterium tuberculosis smear) for detection of active disease.

**Tuberculin Skin Test (TST)**

All subjects were skin tested with 0.1 ml of 5-TU (tuberculin units) PPD injected intradermally according to the Montoux technique. All TSTs were performed by a specialized and experienced nurse from Tuberculosis Control Dispensary, and evaluated by two chest-diseases specialists. All evaluations were performed with palpation and ballotpoint methods along two axes of the forearm, after 72 hours of intradermal injection, and all results were recorded by consensus. The results of the TSTs were considered positive when diameter of induration was ≥15 mm which is the cut-off value for the BCG-vaccinated population according to Control of Tuberculosis Guidelines of the Ministry of Health of Turkey [25]. All TST positive subjects underwent further clinical investigation with symptom query, chest x-ray (and if needed sputum stain for Mycobacterium tuberculosis smear) for detection of active disease.

**Statistical analysis**

“Kolmogorov-Smirnov” and “Shapiro Wilk” tests were used to explore the normality. “Mann-Whitney U test” were performed to compare two groups. “Fisher Exact” and “Pearson Chi Square tests were used to compare QFT-GIT results among occupations, workplaces, working durations. Logistic regression analysis was performed to determine predictors of QFT-GIT positivity. Candidate variables were age (years), work places and duration of work (months).

**Results**

Four volunteers with indeterminate QFT-GIT results (2 doctors, 1 nurse and 1 lab worker) were not included. Thus, 52 (%54.2) females and 44 males (%45.8) constituted the study population, composition of which is shown on Table 1. Ages of the subjects ranged from 21 to 51 years (32.01±6.28, as mean ±SD). The participants had been working at health facilities for 1 to 276 months (89.39±64.79, as mean ±SD).

All of the volunteers have at least 1 BCG scar. There was a statistically significant relation between the number of BCG scars and the diameter of TST. The diameter of TST increases when the number of BCG vaccination rises. Table 2 shows the TST results with respect to BCG scar number, chest x-ray (and if needed sputum stain for Mycobacterium tuberculosis smear) for detection of active disease.

Mean TST diameter in QFT-GIT negative HCWs was significantly smaller than in positive ones (p<0.001). While QFT-GIT results did not significantly differ between doctors, nurses,
it was significantly different between the Health Care Facilities, as employment places (p<0.001, Table 4).

### Table 3. QFT-GIT results with respect to TST diameter.

| TST Diameter | Negative | | | Positive | | | Total |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 0–5 mm | 3 | 100.0 | 0 | 0.0 | 3 | 3.1 |  |
| 6–14 mm | 57 | 93.4 | 4 | 6.6 | 61 | 63.5 |  |
| ≥15 mm | 17 | 53.1 | 15 | 46.9 | 32 | 33.3 |  |
| Total | 77 | 80.2 | 19 | 19.8 | 96 | 100.0 |  |

Chi-square test, p<0.001. QFT-GIT – Quantiferon TB Gold in Tube Test; TST – Tuberculin Skin Test; n – number.
* % with in row; ** % with in column.

### Table 4. QFT-GIT results with respect to variables.

| Variables | Sex | | | Occupation | | | Health care facility | | | Direct contact with TB patient | | | Contact with materials investigated for TB | | | Mean ±SD | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | | | | | | | | | | | | | |
| | Male | 36 | 81.8 | 8 | 18.2 | | | | | | | | | | | | | | |
| | Female | 41 | 78.8 | 11 | 21.2 | | | | | | | | | | | | | | |
| | Doctors | 27 | 79.4 | 7 | 20.6 | | | | | | | | | | | | | | |
| | Nurses | 26 | 78.8 | 7 | 21.2 | | | | | | | | | | | | | | |
| | Lab workers | 16 | 94.1 | 1 | 5.9 | | | | | | | | | | | | | | |
| | Paramedics | 8 | 66.7 | 4 | 33.3 | | | | | | | | | | | | | | |
| | University hospital | 55 | 90.2 | 6 | 9.8 | | | | | | | | | | | | | | |
| | State hospital | 21 | 70.0 | 9 | 30.0 | | | | | | | | | | | | | | |
| | TB-control dispensery | 1 | 20.0 | 4 | 80.0 | | | | | | | | | | | | | | |
| | Yes | 55 | 84.6 | 10 | 15.4 | | | | | | | | | | | | | | |
| | No | 22 | 71.0 | 9 | 29.0 | | | | | | | | | | | | | | |
| | Yes | 20 | 90.9 | 2 | 9.1 | | | | | | | | | | | | | | |
| | No | 57 | 77.0 | 17 | 23.0 | | | | | | | | | | | | | | |

QFT-GIT – Quantiferon TB Gold in Tube Test; n – number; TST – Tuberculin Skin Test; SD – Standard deviation; TB – Tuberculosis.
* % with in line.

Working duration was significantly different between QFT-GIT positive and negative HCWs (Table 4). When all HCWs were divided into 2 groups according to if ever employed in lab-workers and paramedics (p>0.05), it was significantly different between the Health Care Facilities, as employment places (p<0.001, Table 4).
facilities where TB patients directly admitted or referred to (such as TB Control Dispensaries, Chest Diseases’ Hospitals, Respiratory Diseases’ Polyclinics, etc – “Direct contact with TB patient”) or not, and QFT-GIT results were compared, there was no significant difference between these groups (p>0.05, Table 4).

Furthermore, when all HCWs were divided into 2 groups according to if ever been employed at laboratories where “materials (such as sputum, body fluids, biopsy specimen, etc) were investigated for TB” or not, and QFT-GIT results were compared, there was no significant difference between these groups, either (p>0.05, Table 4).

Table 5. TST results with respect to variables.

| Variables                        | TST results | Statistical values |
|----------------------------------|-------------|--------------------|
|                                 | Negative    | Positive           | χ²|p* |
|                                 | n | % | N | % |
| Sex                              |   |   |   |   |
| Male                             | 28 | 63.6 | 16 | 36.4 | χ²=0.34, p=0.56 |
| Female                           | 36 | 69.2 | 16 | 30.8 |
| Occupation                       |   |   |   |   |
| Doctors                          | 20 | 58.8 | 14 | 41.2 | χ²=1.57, p=0.66 |
| Nurses                           | 23 | 69.7 | 10 | 30.3 |
| Lab workers                      | 12 | 70.6 | 5 | 29.4 |
| Paramedics                       | 9  | 75.0 | 3  | 25.0 |
| Health care facility             |   |   |   |   |
| University hospital              | 43 | 70.5 | 18 | 29.5 | χ²=5.3, p=0.07 |
| State hospital                   | 20 | 66.7 | 10 | 33.3 |
| TB-control dispensary            | 1  | 20.0 | 4  | 80  |
| Direct contact with TB patient   |   |   |   |   |
| Yes                              | 20 | 64.5 | 11 | 35.5 | χ²=0.1, p=0.75 |
| No                               | 44 | 67.7 | 21 | 32.3 |
| Contact with materials investigated for TB |   |   |   |   |
| Yes                              | 15 | 68.2 | 7  | 31.8 | χ²=0.03, p=0.23 |
| No                               | 49 | 66.2 | 25 | 33.8 |

| Mean ±SD                       | Mean ±SD |
|--------------------------------|----------|
| Age (years)                    | 30.3±5.3 | 35.3±6.9 | p=0.001 |
| Working duration (months)      | 72.2±56.1| 123.7±68.2| p<0.001 |

TST – Tuberculin Skin Test; n – number; SD – Standard deviation; TB – Tuberculosis. * % with in line.

Table 6. Logistic regression analysis result of some variables that may affect QFT-GIT positivity.

| Variables                        | OR | 95% C.I. for EXP(B) | p |
|----------------------------------|----|--------------------|---|
|                                 |    | Lower              | Upper |
| Age (years)*                     | 0.970 | 0.826                | 1.139 | 0.709 |
| Health care facility             |    |                    |       |
| University hospital              | 1  |                    |       |
| State hospital                   | 2.708 | 0.797                | 9.201 | 0.110 |
| TB-control dispensary            | 22.050 | 1.355               | 358.855 | 0.030 |
| Working duration (months)*       | 1.017 | 1.002                | 1.033 | 0.031 |

*Age and duration of work are not weighted.
These variables were also analyzed with respect to TST positivity and all, except age and working duration, were similar in negative and positive TST groups (Table 5).

Some variables (age, work places and working duration) that showed significant difference between QFT-GIT positive and negative results were further investigated by logistic regression analysis (Table 6). On logistic regression, working at the TB-Control Dispensary (Odds ratio-OR: 22.05) and duration of work (OR: 1.017) were found to affect the QFT-GIT positivity, significantly (Table 6).

The concordance between QFT-GIT and TST was found to be 78.1% with a Kappa statistic value of 0.452 which represents a “moderate” concordance (Table 7). Prevalence of LTBI in the study population was 19.8% according to QFT-GIT test and 33.3% according to TST. BCG vaccination rate was %100.

Discussion

HCWs are one of the groups at-risk for *M. tuberculosis* infection. However, the level of TB exposure varies widely among various health care occupations [25]. In many developed countries, such as United States and Canada, HCWs are screened by TST to identify and to treat LTBI [26]. However, effective screening requires a test that can accurately and reliably diagnose LTBI and predict those most likely progress to disease [27]. Although the TST has been useful tool to detect LTBI, for more than a century, it has several biologic and operational limitations, namely, properly administering the intradermal injection, need for the TST reading, reader variability, variable specificity, cross-reactivity with BCG vaccine and NTM infection. Furthermore TST is not adequate for the diagnosis of LTBI in populations with high BCG coverage and/or high level of NTM exposure [28].

It has been reported that repeated vaccinations have more persistent affect on TST [29]. In our study, there was a statistically significant relation between the number of BCG scars and the diameter of TST. Furthermore, an increase in the TST diameter was associated with an increase in the number of QFT-GIT positive cases, although we did not investigate the correlation between the diameter of TST and the magnitude of QFT response (Table 3). Furthermore we found that mean TST diameter in QFT-GIT negative HCWs was significantly smaller than in QFT-GIT positive ones (Table 4). In a study carried out by Pottumathry et al., it was showed that correlation between the diameter of Mantoux test’s induration and magnitude of the QFT was significant and of moderate strength in HCWs [30]. In contrast, Johnson et al. and Fietta et al. did not report any correlation between the diameter of TST and the magnitude of QFT response [31,32]. The difference between these reports may be because of different immunities in participants, as well as other factors such as endemicity for TB, the frequency of BCG vaccination, and exposure to environmental *Mycobacterium* spp. in the countries examined.

Many reports have showed that increased age, working as an elderly, more years in health care profession, working in a high-risk department, collaborating in high risk procedures and frequent contact with tuberculosis patients had been the risk factors associated with higher prevalence of positive results on QFT test in HCWs [33–37].

In this study HCWs with positive QFT-GIT results were significantly older than the ones with negative results. Furthermore duration of work was significantly longer in QFT-GIT positive than in negative HCWs. Both findings indicate that QFT-GIT positivity, in other words risk of LTBI, become higher with age and with time spent in profession.

We found that QFT-GIT results did not significantly differ between doctors, nurses, lab-workers and paramedics. On the other hand, QFT-GIT results significantly different between the Health Care Facilities, as employment places. Most prominent QFT-GIT positivity was present in the HCWs from TB-Control Dispensary where all cases suspected to have any form of TB were referred to, thus increasing direct contact risk for employees.

On logistic regression, working at the TB-Control Dispensary (Odds ratio-OR: 22.05) and duration of work (OR: 1.017) were found to be the significant risk factors affecting the QFT-GIT positivity.

Interestingly, when all HCWs were divided into 2 groups according to if ever been employed in facilities where TB patients directly admitted or referred to (such as TB Control Dispensaries, Chest Diseases’ Hospitals, Respiratory Diseases’ Polyclinics, etc.-i.e. facilities with High risk of direct contact, Group 1), or not (facilities with no high risk, Group 2), and QFT-GIT results

| Table 7. The concordance between QFT-GIT and TST. |
|-----------------------------------------------|
| **QFT-GIT** | **TST** | **Kappa statistic** |
| **Negative** | **Positive** | |
| Negative | Negative | 60 | 17 | 0.452 |
| Positive | Positive | 4 | 15 | |
| Total | | 64 | 32 | |

* TST <15 mm; * TST ≥15 mm; a kappa statistic of ≥0.75 represents excellent concordance, 0.40≤ Kappa <0.75 represents good to fair concordance, and kappa <0.40 represents poor concordance.
were compared, there was no significant difference between group 1 and 2 (p>0.05, Table 4). Furthermore, when all HCWs were divided into 2 groups according to if ever been employed at laboratories where materials (such as sputum, body fluids, biopsy specimen, etc) were investigated for TB (high risk of contact, Group A), or not (no high risk, Group B), and QFT-GIT results were compared, there was no significant difference between these groups, either (p>0.05, Table 4).

Keskiner et al. had stated that the factors determining TST positivity among HCWs differ in developed and in developing countries [38]. In developing countries, such as Turkey, relatively higher prevalence rates of TB and of BCG vaccination are challenges for studies in this field [23]. BCG vaccination rate was %100 in our study population and 70 of HCWs had multiple vaccinations (Table 2). BCG vaccination is part of the national vaccination program of Turkey, although it has not been integrated as a routine practice for HCWs. BCG is administered to new-borns and to 6 years’ old children. Two more BCG at ages of 11 and 16 had also been administered before 1996. Therefore, six of subjects in our study group had 3 BCG vaccinations and one has 4. To overcome false positivity due to BCG vaccination, some authors have defined TST positivity as an induration of 15 mm or more for individuals from developing countries, as is the case according to Control of Tuberculosis Guidelines of the Ministry of Health of Turkey [25,39,40].

If induration’s diameter of TST ≥15 mm was considered to be “positive” – which is the case in the BCG-vaccinated population according to Control of Tuberculosis Guidelines of the Ministry of Health of Turkey [25] – concordance between QFT-GIT and TST was found to be 78.1% with a Kappa statistic value of 0.452 which represents a moderate concordance (Table 7).

Pottumarthy et al., Pai et al., and Katial et al., found a good concordance between QFT-GIT and TST, when a positive TST reaction was defined as the diameter of induration ≥15 mm [30,33,41]. Pai et al. determined that BCG vaccination had little impact on the results of either test [33]. The differences between their findings and ours could be explained by different prevalence of exposure to TB in the study subjects and by multiple BCG vaccination in our study population. On the hand, Ozdemir et al. and Mahomed et al. showed a poor concordance between QFT-GIT and TST [24,42]. The difference in concordance between QFT and TST in these studies may have been related to differences in the immunology of participants and to the better sensitivity and specificity of QFT than TST. In addition, while the biological determinants of QFT and TST assays are similar, they are not equivalent. If both tests have comparable sensitivity, the level of concordance between the tests is likely to increase as the TB prevalence (and therefore the number of true-positive results) in a population increase [43]. Concordance would, therefore, be lower in low-prevalence populations with a comparable proportion of confounding factors, such as BCG vaccination, that might influence the result of one test (TST) but not the other (QFT-GIT).

Prevalence of LTBI in the study population was 19.8% according to QFT-GIT test and 33.3% according to TST. These different values may be explained by the fact that QFT-GIT eliminates the potential for false-positive results caused by previous BCG vaccination(s) [44,45]. Despite all advantages of QFT-GIT over TST, it may still lead to “indeterminate” or “borderline” results, using cutoff values specified by the FDA, although quantitative results could theoretically be reported as well. One of the questionable points regarding our QFT-GIT test might be unconsidered quantitative results. On the other hand, large clinical experience indicates that “indeterminate” or “borderline” results, usually the result of a technical problem in the laboratory or failure of the positive control to stimulate IFN-γ production, occur only 2% to 4% of the time in good laboratories (46). The chief operational limitation posed by the QFT-GIT test is its cost, which is substantially more than a TST. It also requires equipment and consumables that translate into high costs for the health system [46].

**Conclusions**

In conclusion, TST is affected by previous BCG vaccinations and number of cases with QFT-GIT positivity is increased in accordance with the TST induration diameter range. Working duration and working at the TB-Control Dispensary are the significant risk factors affecting the QFT-GIT positivity. We suggest that QFT-GIT can be used as an alternative to TST for detection of LTBI especially in risk groups of a population with relatively high incidence of TB and with routine BCG vaccination program. Besides, large-scale trials with quantitative measurements of QFT-GIT are also needed, possibly to well establish different cut-off values for different high risk groups for LTBI.

A simple, head to head comparison of the QFT-GIT and the TST is prevented by lack of a gold standard for diagnosis of TB infection. In light of this, the most efficient and meaningful assessment of these tests would involve assembling cohorts of people (such as contacts, immunosuppressed people, HCWs), testing them for TB infection, and observing them over time, untreated, to determine which assay most accurately predicts in which people active TB develop [45]. However, the logistical and ethical issues raised by such a study design are complex.
References:

1. World Health Organization: Global tuberculosis control: epidemiology, strategy, financing: WHO report 2009. Geneva, Switzerland: World Health Organization, 2009.

2. Kantor HS, Poblete R, Pusateri SJ: Nosocomial transmission of tuberculosis from unsuspected disease. Am J Med, 1998; 84: 833–88.

3. Alfonso-Echonove I, Granich RM, Laszlo LA et al: Occupational transmission of Mycobacterium tuberculosis to health care workers in a university hospital in Lima, Peru. Clin Infect Dis, 2001; 33: 589–96.

4. Tam CM, Leung CC: Occupational tuberculosis: a review of the literature and the local situation. Hong Kong Med J, 2006; 12: 448–55.

5. Centers for Disease Control and Prevention. Expanded tuberculosis surveillance and tuberculosis morbidity-United States 1993. MMWR Mortal Wkly Rep, 1994; 43: 361–66.

6. Menzies D, Pai M, Comstock G: Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med, 2007; 146: 340–54.

7. Richelhi L: An update on the diagnosis of tuberculosis infection. Am J Respir Crit Care Med, 2006; 174: 736–42.

8. Trajman A, Steffen RE, Menzies D: Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. Pulm Med, 2013; 8(4): e59546.

9. Tissot F, Zanetti G, Francioli P et al: Influence of Bacilli Calmette-Guerin vaccine on size of tuberculin skin test reaction: to what size? Clin Infect Dis, 2005; 40: 211–17.

10. Pai M, Kalantari S, Dheka H: New tools and emerging technologies for the diagnosis of tuberculosis: Part I. Latent tuberculosis. Expert Rev Mol Diag, 2006; 6: 413–22.

11. Passaïent L, Khan K, Richardson R et al: Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the TSPOT. TB test, tuberculin skin test, and an expert physician panel. Clin J Am Soc Nephrol, 2007; 2(1): 68–73.

12. Pai M, Dheka H, Cunningham J et al: T-cell assays for the diagnosis of latent tuberculosis infection: moving the research agenda forward. Lancet Infect Dis, 2007; 7: 428–38.

13. Mazurek GH, LoBue PA, Daley CL et al: Comparison of wheeze blood interferon gamma assay with tuberculin skin testing for detecting latent Mycobacterium tuberculosis infection. JAMA, 2001; 286: 1740–47.

14. Arend SM, Thijssen SF, Leyten EM et al: Comparison of two interferon gamma assays and tuberculin skin test for tracing tuberculosis contacts. Am J Respir Crit Care Med, 2007; 175: 618–27.

15. Dogra S, Narang P, Mendiratta DK et al: Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India. J Infect, 2007; 54: 267–76.

16. Tsouiri S, Austin J, Toro P et al: Results of a tuberculosis-specific IFN-gamma assay in children at high risk for tuberculosis infection. Int J Tuberc Lung Dis, 2006; 10(8): 939–41.

17. Sobor B, Andersen AB, Larsen HK et al: 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, 2007; 39: 554–59.

18. Kobashy M, Mouri K, Obayek E et al: Clinical evaluation of Quantiferon-TB IN-Tube test for immunocompromised patients. Eur Respir J, 2007; 30(5): 945–50.

19. Caglayan V, Ak O, Dabak G et al: Comparison of tuberculin skin testing and QuantiFERON-TB Gold test for detecting active tuberculosis. Med J Hosp Med, 2012; 7(5): 377–81.

20. Tan LH, Kamratzam A, Liam CK et al: Tuberculin skin testing among healthcare workers in the University of Malaya Medical Centre, Kuala Lumpur, Malaysia. Infect Control Hosp Epidemiol, 2002; 23(10): 584–90.

21. Katial RR, Hershey J, Purushoth-Seth T et al: Cell-mediated immune response to tuberculosis antigens: Comparison of skin testing and measurement of in vitro gamma interferon in whole-blood culture. Clin Diag Lab Immunol, 2001; 8: 347–53.

22. Mahomed H, Hughes EJ, Hawkridge T et al: Comparison of Mantoux skin test with three generations of a whole blood IFN-gamma assay for tuberculosis infection. Int J Tuberc Lung Dis, 2005; 9: 313–19.
44. 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.

45. Schluger NW, Burzynski J: Recent advances in testing for latent TB. Chest, 2010; 138(6): 1456–63.

46. Steffen RE, Caetano R, Pinto M et al: Cost-effectiveness of Quantiferon(R)-TB Gold-in-Tube versus tuberculin skin testing for contact screening and treatment of latent tuberculosis infection in Brazil. PloS One, 2013; 8(4): e59546.