Screening of latent tuberculosis infection among health care workers working in Hajj pilgrimage area in Saudi Arabia, using interferon gamma release assay and tuberculin skin test

Zakeya A. Bukhary,a Soliman M. Amer,b Magdy M. Emara,a Mohammad E. Abdalla,a Sahar A. Ali c

From the aDepartment of Internal Medicine, Taibah University, Madina, Saudi Arabia; bDepartment of Public Health and Community Medicine, Alazhar University, New Damietta, Egypt; cDepartment of Microbiology and Immunology, Menoufiya University, Menoufiya, Egypt

BACKGROUND: Interferon gamma release assays (IGRA) is highly specific for Mycobacterium tuberculosis and is the preferred test in BCG-vaccinated individuals. The few studies that have screened health care workers (HCWs) in Saudi Arabia for latent tuberculosis infection (LTBI) using IGRA have varied in agreement with the traditional tuberculin skin test (TST).

OBJECTIVE: Assess the prevalence of LTBI among HCWs working in the Hajj pilgrimage using IGRA and TST and measuring their agreement.

DESIGN: Cross-sectional prospective.

SETTING: Multiple non-tertiary care hospitals.

PATIENTS AND METHODS: HCWs who worked during the Hajj pilgrimage in Saudi Arabia in December 2015. Data was collected by standardized questionnaire. Samples were drawn and analyzed by standard methods.

MAIN OUTCOME MEASURES: The prevalence of LTBI among HCW and the agreement by kappa statistic between QFT-GIT and TST.

SAMPLE SIZE: 520 subjects.

RESULTS: The sample included 30.7% nurses and 19.2% physicians. The majority were BCG vaccinated (98.5%). There were a total of 56 positive by QFT-GIT and the LTBI rate was 10.8%. In 50 QFT positive/476 TST negative the LTBI rate was 10.5% in discordant tests, and in 6 QFT positive/44 TST positive it was 13.6% in concordant tests. The overall agreement between both tests was poor—83% and kappa was 0.02. LTBI prevalence was associated with longer employment (13.1 [9.2] years). The QFT-GIT positive test was significantly higher in physicians (P=0.02) and in HCWs working in chest hospitals 16/76 (21.05%) (P=0.001).

CONCLUSION: Agreement between the tests was poor. QFT-GIT detected LTBI when TST was negative in HCWs who had a history of close contact with TB patients.

LIMITATIONS: A second step TST was not feasible within 2-3 weeks.

CONFLICT OF INTEREST: None.
Interferon gamma release assays (IGRA), particularly the QuantiFERON Gold in Tuberculosis (QFT-GIT) test, are the preferred diagnostic tools for screening of latent tuberculosis infection (LTBI) in health care workers (HCWs) working in tertiary care hospitals. Several systematic reviews have suggested that IGRA are as sensitive and more specific than TST in identifying high-risk people for TB infection particularly in low incidence areas. The sensitivity of QFT has been consistently reported as 81% to 86%, equal to the sensitivity of the TST (71%-82%). However, the specificity of QFT has been high (94-98%) compared to a low TST specificity (47-70%) in BCG-vaccinated individuals. TB in Saudi Arabia has a moderate incidence rate of 10 per 100,000 population according to World Health Organization (WHO) reports in 2017. Close contacts and mass-gathering from all over the world during Hajj pilgrimage can potentially transmit airborne diseases such as Mycobacterium tuberculosis (MTB) infection to HCWs. Annual screening of LTBI using TST traditionally can detect TB infection among HCWs with high occupational risk, especially those who provide care during Hajj pilgrimage. The use of IGRA for routine screening of HCWs remains an area of controversy and many international guidelines (Europe and Canada) have not endorsed IGRA alone for testing in a healthcare setting.

IGRA is a single blood test that measures the T-cell-mediated immune response and the interferon (IFN)-gamma release following incubation with MTB-specific antigens. There are two commercial QFT tests (QFT-GIT and TB spot). The QFT-GIT assay is an enzyme-linked immunosorbent assay (ELISA)-based, whole-blood test that uses peptides from three TB antigens (ESAT-6, CFP-10, and TB7.7) in an in-tube format. The result is reported as quantification of interferon (IFN)-gamma in international units (IU) per mL. The TB spot test is preferable in immunocompromised patients. IGRA advantages include convenient or favorable fast results with no follow-up visit required to complete the testing process, especially for the busy HCWs. There are no false-positive results in prior BCG-vaccinated individuals or those who are previously sensitized with non-tuberculous mycobacterium (NTM). IGRA overcome the challenges related to TST for the screening of LTBI such as the use of injection, inconvenient return in 48-72 hours for reading of results, the process of training HCWs for proper test performance and the inter-reader variability in interpretation. TST is a delayed-type hypersensitivity response to the purified protein derivative (PPD) of MTB, with false positive results in individuals who are previously BCG vaccinated or with NTM infection, and has a low sensitivity for active TB.

Local Saudi guidelines on the management of latent tuberculosis do not recommend using IGRA for the diagnosis of active tuberculosis. The positive predictive value of IGRA is low because it does not differentiate between active TB disease and LTBI. As it is controversial, authors think clinical action is necessary following the positive IGRA to rule out active TB disease. Other limitations include the reproducibility of results in different laboratories, blood collection and samples processing. Our objective was to assess the prevalence of LTBI among HCWs working in Hajj pilgrimage using QFT-GIT test and TST and to measure the association or agreement of the two tests.

PATIENTS AND METHODS
Any physician, nurse or other HCW who did not have a positive TST and who worked in the Hajj pilgrimage during their employment were invited to participate voluntarily in the study. The enrollment period began after the Hajj and last for three months. Inclusion criteria required that participants be HCWs who previously worked in the Hajj pilgrimage, 22 years of age or older, employed for more than two years, and not have had close contact with pulmonary TB patients within the previous three months. Exclusion criteria included pregnancy, immunoinconpetency, employment as administrative staff, contact with a pulmonary TB patient within the previous three months), or a recent history of a positive TST. The research was approved by the Deanship of Research in Taibah University#3104/435 and approved by the IRB and deanship of research through the scientific ethical committee.

A data collection questionnaire designed by the investigators was used to collect information by face-to-face interview on gender, age, nationality, workplace, job classification, duration of employment in hospitals, BCG vaccination, history of contact with TB patients and history of associated co-morbidity. Data were collected by trained investigators and entered into the computer for statistical analysis by different investigators. An investigator blinded to the data collection or interviews did the data analysis. The clinical evaluation was done in the clinic by separate physician investigators. Investigators were supervised by the primary investigator at the beginning of data collection to ensure that instructions and questions were clear to investigators and participants.
Blood volumes were collected by a trained HCW after informed consent was obtained from all participants and just before TST performance. Three mL of whole blood was collected from each participant. For the QuantiFERO-TB Gold In-Tube test (QFT-GIT), 1 mL delivered into each of the three tubes labeled as nil control, positive control and M tuberculosis specific antigens (ESAT-6 and CFP10). The blood was incubated without delay, with the test antigens ≤12 hours after collection. Tubes were incubated at 37°C overnight for 16–24 before centrifugation. QFT-GIT kits (Cellestis Limited, Carnegie, Australia) contain three types of tubes, the M tuberculosis specific antigens tubes which include two mixtures of synthetic peptides representing ESAT-6 and CFP10 as test antigens, phytohemagglutinin (a mitogen used as a positive assay control), and saline (used as a nil sample to measure the background level of IFN-g).

After incubation, the concentration of IFN-gamma in the plasma is determined by ELISA, using the reagents included in the test kit and the PEB III (Dade Behring). The amount of IFN-gamma released is determined by subtracting the amount in the nil tube from the amount in the ESAT-6, CFP-10, or mitogen-stimulated plasma.

The IFN-gamma response in the negative control). TST uses a single step 0.1 mL (2 TU) of purified protein derivative (RT23; Copenhagen, Denmark) intradermal injection on the volar side of the forearm, and the transverse diameter of the induration was read 48 to 72 h later. An induration of 10-mm diameter or more was considered positive. Challenges included lab transportation with out delay, and the concern of some HCW over accidental venipuncture.

The data were analyzed using statistical analysis software package SPSS version 16 (https://www.ibm.com/products/spss-statistics). The authors were blinded to results. Data is presented as frequencies, mean and standard deviation as appropriate. The Chi-square and the Fisher exact test were used to test the significance between the qualitative variables. The independent t test used to test the significance between the quantitative variables. P value ≤.05 was considered of statistically significant. The agreement between QFT-GIT and TST was assessed by kappa where κ>0.75 represent excellent agreement, κ values from 0.4–0.75 represent fair to good agreement and κ< 0.4 represent poor agreement.30,31

### RESULTS

The study included 520 HCWs from Saudi Arabia working at multiple secondary care hospitals and the Haj pilgrimage region. The mean (SD) age was 34.9 (9.7) years with the youngest 22-years-old and the eldest of 62 years old. There were 66.9% males, and 33.1% females. The majority were non-Saudi, mainly from Egypt (17.1%) Philippines (15.2%), Bangladesh (12.3%), Sudan (3.2%) and others from Yemen, Syria, and India (9.6%) (Table 1). Of the 520 HCWs enrolled 50% were clinical staff involved with direct patient care. The mean (SD) length of employment was 10.3 (9.3) years. Most worked in secondary care non-chest hospitals. The majority of studied population had a history of BCG vaccination and almost half had had close contact with TB patients. Only 8.5% had a positive TST, and all had a normal chest X-ray (CXR).

A total of 56/520 (10.8%) had a positive QFT-GIT (Table 2). All HCWs with a positive TST or QFT-GIT were avoided and all samples were incubated less than 12 hrs after collection in a standard single laboratory. A history of BCG was determined and all participants who had positive TST or positive QFT-GIT test were assessed with recent chest X-ray reviewed with the infectious diseases specialist to rule out active TB diseases. Blood sampling was done just prior to TST. An individual is considered positive for M. tuberculosis infection if the IFN-gamma response to TB antigens is above the test cut-off (after subtracting the background IFN-gamma response in the negative control). TST uses a single step 0.1 mL (2 TU) of purified protein derivative (RT23; Copenhagen, Denmark) intradermal injection on the volar side of the forearm, and the transverse diameter of the induration was read 48 to 72 h later. An induration of 10-mm diameter or more was considered positive. Challenges included lab transportation without delay, and the concern of some HCW over accidental venipuncture.

### Table 2

| Interpretation Criteria for QFT-GIT | TB Specific Antigen Response (IU/mL)* | Nil Control (IU/mL) | Mitogen Control (IU/mL)* |
|------------------------------------|--------------------------------------|---------------------|--------------------------|
| Positive                           | ≥ 0.35 (and ≥ 25% of Nil)            | ≤ 8.0               | any                      |
| Negative                           | < 0.35 (or < 25% of Nil)             | ≤ 8.0               | ≥ 0.5                    |
| Indeterminate                      | < 0.35 (or < 25% of Nil)             | ≤ 8.0               | < 0.5                    |
| any                                | > 8.0                                | any                 |

*Corrected for nil response.30 A summary of meeting proceedings on addressing variability around the cut point in serial interferon-γ release assay testing. Infect Control Hosp Epidemiol 2013; 34:625-630.

QFT-GIT results were calculated quantitatively, using the software in the manufacturer guidelines to interpret test results, as shown in the interpretation criteria table. The QFT was considered positive or negative based on the IFN-concentration cut off value of 0.35 IU/mL, using the interpretation criteria in the interpretation criteria table.30

The anticipated practical limitations of QFT-GIT were avoided and all samples were incubated less than...
were assessed with CXR, and the data collected for the study. The clinical well-being and normal radiology was documented for the diagnosis of LTBI in this group of HCWs. The mean age was significantly higher in QFT-GIT positive participants compared to QFT-GIT negative participants ($P=.01$). There was no statistically significant differences in QFT-GIT test results among Saudis versus non-Saudis. (Table 2). QFT-GIT positive was significantly higher in physicians compared with other job classifications ($P=.02$). The QFT-GIT positive test was higher in HCWs working at chest hospitals than HCWs in other hospitals ($P=.001$). The duration of employment was significantly longer in QFT-GIT positive participants compared to the others ($P=.02$). There was no difference in close contact with TB patients. There was also no significant associated comorbidity, such as diabetes or chronic steroid use, among the QFT-GIT HCWs. The majority of HCWs with positive QFT-GIT results had a negative TST. Concordant results were obtained in 13.6% of TST positive/QFT positive cases and 89.5% of TST negative /QFT negative cases (Table 2). TST positive/QFT negative discordance was 86.4% while TST negative/QFT positive discordance was 10.5%. The overall agreement between results of two tests was 83%, with a kappa 0.02 which is considered poor agreement ($κ<0.4$) (Table 3).

**DISCUSSION**

Respiratory infections and communicable diseases are challenging hazards to HCWs, especially with the close contact that occurs during mass gathering like the Haj pilgrimage. There are few studies in Saudi Arabia with variable agreement using both (QFT-GIT and TST) as risk assessment methods for TB infection. The agreement between (QFT-GIT and TST) in pre-employment screening for HCWs, and in post-exposure screening has been reported as fair to good. These studies were implemented on geographically diverse study populations at tertiary care hospitals. The association or agreement between both methods (QFT-GIT and TST) was different in other studies, with poor agreement in renal dialysis, and renal transplant patients. The HCWs working in Hajj pilgrimage area with LTBI in our study (10.5%) had discordant results for QFT-GIT positive/TST negative (50/476). There were 6 (13.6%) HCWs with concordant QFT-GIT positive/TST positive (6/44). In two different studies in Saudi Arabia, the prevalence of LTBI using both QFT and TST was 31.5% in 2012-2015 compared to 11% using TST alone in 2010.

The overall poor agreement between both tests is consistent with a tertiary care study in Saudi Arabia in

| Characteristics | Number (percent) or mean (SD) |
|-----------------|-------------------------------|
| Sex             |                               |
| Males           | 348                           |
| Females         | 172                           |
| Age (range) (years) | 34.9 (9.7), 22-62            |
| Nationality     |                               |
| Saudi           | 221                           |
| Non-Saudi       | 299                           |
| Job classification |                             |
| Physician       | 100                           |
| Nurse           | 160                           |
| Pharmacist      | 70                            |
| Lab. Technicians| 50                            |
| Housekeeper     | 70                            |
| Radiology Technicians | 70                  |
| Duration of employment (years) | 10.3 (9.3)            |
| Diabetes mellitus type 2 |                     |
| Yes             | 24                            |
| No              | 496                           |
| Use of steroid  |                               |
| Yes             | 4                             |
| No              | 516                           |
| BCG vaccine     |                               |
| Yes             | 512                           |
| No              | 8                             |
| Contact with TB patient in the past (more than 12 weeks prior to participation in the study) | |
| Yes             | 200                           |
| No              | 320                           |
| Type of hospital place of work |                     |
| Chest hospital (Pilgrims hospital) | 76                  |
| Multicenter non chest hospitals-secondary care | 444                  |
| Tuberculin skin test |                             |
| Positive (more than or equal to 10 mm induration) | 44                  |
| Negative (less than 5 mm induration) | 476                  |

Data are mean (standard deviation) or number (percentage).
### Table 2. Factors tested for significant association with positive QFT-GIT results.

| Variable                          | Positive QFT-G N=56 (10.77%) | Negative QFT-G N=464 (89.23%) | Total  | P value |
|-----------------------------------|-----------------------------|--------------------------------|--------|---------|
| Mean age in years (SD)            | 38.0 (10.3)                 | 34.5 (9.6)                     |        | .01     |
| Sex                               |                             |                                |        |         |
| Males                             | 46                          | 13.2                           | 302    | 86.8    | 348    | .01     |
| Females                           | 10                          | 5.8                            | 162    | 94.2    | 172    |         |
| Nationality                       |                             |                                |        |         |
| Saudi                             | 28                          | 12.7                           | 193    | 87.33   | 221    | .25     |
| Non Saudi                         | 28                          | 9.3                            | 271    | 90.7    | 172    |         |
| Job classification                |                             |                                |        |         |
| Physician                         | 20                          | 20.0                           | 80     | 80.0    | 100    | .02     |
| Nurse                             | 12                          | 7.5                            | 148    | 92.5    | 160    |         |
| Pharmacist                        | 4                           | 5.7                            | 66     | 94.3    | 70     | .02     |
| Lab. Technicians                  | 4                           | 8.0                            | 46     | 92.0    | 50     |         |
| Housekeeper                       | 10                          | 14.3                           | 60     | 95.0    | 70     |         |
| Radiology technicians             | 6                           | 8.7                            | 64     | 85.7    | 70     |         |
| Duration of employment in years   | 13.1 (9.8)                  | 10.0 (9.1)                     |        | .02     |
| Diabetes mellitus type 2          |                             |                                |        |         |
| Yes                               | 4                           | 16.7                           | 20     | 83.3    | 24     | .34     |
| No                                | 52                          | 10.5                           | 444    | 89.5    | 496    |         |
| Use of steroid                    |                             |                                |        |         |
| Yes                               | 0                           | 0.0                            | 4      | 100.0   | 4      | .69     |
| No                                | 56                          | 10.9                           | 460    | 89.1    | 516    |         |
| BCG vaccine                       |                             |                                |        |         |
| Yes                               | 56                          | 10.9                           | 456    | 89.0    | 512    | .32     |
| No                                | 0                           | 0.0                            | 8      | 100.0   | 8      |         |
| Contact with TB patient           |                             |                                |        |         |
| Yes                               | 22                          | 11.0                           | 178    | 89.0    | 200    | .89     |
| No                                | 34                          | 10.6                           | 286    | 89.4    | 320    |         |
| Type of hospital                  |                             |                                |        |         |
| Chest hospital (Pilgrims hospital) | 16                          | 21.1                           | 60     | 79.0    | 76     | .001    |
| Multi center non chest hospitals  | 40                          | 9                              | 404    | 91.0    | 444    |         |
| Tuberculin skin test              |                             |                                |        |         |
| Positive                          | 6                           | 13.6                           | 38     | 86.4    | 44     | .609    |
| Negative                          | 50                          | 10.5                           | 426    | 89.5    | 476    |         |

Data are mean (standard deviation) or number (percentage)
2017 by Edathodu et al, who evaluated the diagnostic potential of interferon-gamma release assay to detect latent tuberculosis infection in kidney transplant recipients with similar poor agreement.\textsuperscript{36}

To our knowledge, our study is the second largest following another large one.\textsuperscript{4} Our study was a cross-sectional, prospective screening of LTBI in HCWs in Saudi Arabia using IGRA and TST, which measured the association and assessed the poor agreement between both QFT-GIT and TST. We found similar numbers of QFT positive HCWs among Saudis and non-Saudis, indicating little apparent difference among nationalities. Occupational hazards such as being a HCW, longer employment, and working in areas of mass gathering were associated with higher prevalence of LTBI, which was mainly diagnosed using QFT-GIT regardless of the nationality or the geographical origin of HCWs. The pattern of discordant positive QFT-GIT/negative TST was significantly affected with the job category, with physicians differing from others. Working in a chest hospital was associated as a major risk of TB exposure and LTBI compared to non-chest hospitals. Subjects with LTBI had higher mean duration of employment. Based on the annual risk of TB in the studied population, TB guidelines and TB program, all HCWs have a moderate probability of TB transmission, considered to be high in chest hospitals.\textsuperscript{9}

Physicians in this study were fewer in number than nurses (100/160) when compared to the literature, where nurses were found to be the profession associated with the most concordant results and physicians were the least with discordant positive QFT-GIT/negative TST.\textsuperscript{4} However, in El Helaly et al retrospective pre-employment screening of HCWs job type or being with clinical vs non-clinical profession was not associated with concordant results of both tests.\textsuperscript{3}

Findings in this study involving HCWs with medium-to-high occupational risk, and who were in majority BCG vaccinated can be explained by the the biologic limitations and the waning immunity of BCG routinely given immunization at birth or in infancy or early childhood;\textsuperscript{38,39} the negative TST is unlikely to be due to technical limitations, IGRA being approved in the literature with specificity of 98.1% and a sensitivity of 89.0%;\textsuperscript{40-42} IGRA not affected by BCG vaccination status and when 13.63 % of the study population had concordant positive QFT-GIT with TST positive they were more useful for evaluation of LTBI.\textsuperscript{43}

The strengths of this study were that screening using QFT-GIT enabled the detection of 10.5% of positive HCWs with LTBI. In addition, blood sampling for QFT-GIT was done just before the TST, so QFT-GIT was an alternative method to detect LTBI when TST was negative. No intermediate results were reported for QFT-GIT. Our investigators were carefully trained for performing the TST. The IGRA results were measured quantitatively by the lab and reported qualitatively as positive/negative. The interpretation of IGRA results was carried out according to the clinical profile and radiologic assessment of each participant among HCW, and consequently the analysis of results were more thorough and required longer time. Our subjects were studied prospectively and are the most recent representative sample when compared to previous studies in Saudi Arabia, where subjects were enrolled either retrospectively, or before the date of this study.\textsuperscript{3,35,36,37}

The window period required for QFT to be positive post-exposure was carefully considered when subjects were enrolled in the study since TB exposure within 3 months was the criteria for enrollment. Our results reflect LTBI with little likelihood of false positive and false negative with IGRA specificity of 98.1% and a sensitivity of 89.0%.\textsuperscript{41-43} All TST negative results were based on less than 5 mm of induration, and all positive greater than or equal to 10 mm. There were no intermediate positive results from 5 to 9 mm. A limitation of the study is that the second step TST in HCWs was not feasible within 2-3 weeks when TST was negative.

In conclusion, the prevalence of LTBI in HCWs using QFT-GIT was 10.5% and was higher in physicians with longer duration of employment and working in chest hospitals. The QFT-GIT and TST results were in poor agreement. QFT-GIT positive detected LTBI when TST was negative in HCWs who had a history of close contact with TB patients.
references

1. Lewisohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official american thoracic society/infectious diseases society of america/centers for disease control and prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis 2017; 64:111.
2. Pai M, Kunimoto D, Jameson F, Menzies D. Diagnosis of HCW: Measurment of Infection. Canadian TB Standards, 7th Edition. Can J Infect Dis 2016;7:1-3.
3. El-Helaly M, Khan W, El-Saied A, Balkhy HH. Pre-employment screening of latent tuberculosis infection among healthcare workers using tuberculin skin test and QuantiFERON-TB Gold test at a tertiary care hospital in Saudi Arabia. J Infect Public Health. 2014;7(6):481-488.
4. Al Hajjoj S, Varghese B, Datjjan A, Shoukri M, Alzahrani A, Alkhazen A, et al. Interferon gamma release assay versus tuberculin skin test among healthcare workers of highly diverse origin in a modern hospital in Saudi Arabia. J Infect Public Health. 2014;7(6):481-488.
5. Shoukri M, Alzahrani A, Alkhenizan A, et al. Interferon gamma release assay versus tuberculin skin test and QuantiFERON-TB Gold test at a tertiary care hospital in Saudi Arabia. J Infect Public Health. 2013;6(3):166-72.
6. Canadian Tuberculosis Committee. Updated recommendations on interferon-gamma release assays for latent tuberculosis infection. Ann Canadian Health Care workers using interferon-gamma release assays. PLoS ONE 2012;7(8):e43014.
7. Pai M, Behr M. Latent Mycobacterium tuberculosis infection and interferon-gamma release assay: a diagnostic tool for latent tuberculosis infection in healthcare workers. Memish ZA: Infection control in Saudi Arabia. 2011. http://ecdc.europa.eu/en/publications/Publications/1103_GUI.IGRA.
8. Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculous infection. Lancet 2000; 356(9235):1099-1104.
9. Arend SM, Meijgaard KEN, Boer K, de Palou EC, Soolinglen D, Ottenhoff TH, et al. Tuberculin skin testing and in vitro T cell responses to ESAT-6 and culture filtrate protein 10 after infection with Mycobacterium marium or M. kansasii. J Infect Dis 2002;186(12):1797-1807.
10. Pai M, Gokhale K, Joshi R, Dogra S, Kalsant L, Mandratta DK, et al. Mycobacterium tuberculosis infection in healthcare workers in rural India: comparison of a whole-blood interferon-gamma assay with tuberculin skin testing. JAMA 2005;293(22):2746-2755.
11. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim YS, 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;293(22):2756-2761.
12. Harada N, Nakajima Y, Higuchi K, Sekiya Y, Rothel J, Mori T. Screening for tuberculosis infection using whole-blood interferon-γ release tests among Japanese healthcare workers. Infect Control Hosp Epidemiol 2006;27(5):442-448.
13. Al Jahdali H, Alzahrani A, Alzahrani S, Abba AA, Memish ZA, Alrajhi AA, et al. Saudi guidelines for testing and treatment of latent tuberculosis infection. Ann Saudi Med. 2010;30(1):38-49.
14. Pai M, Behr M. Latent Mycobacterium tuberculosis infection and interferon-gamma release assays. Microb Spec 2016;495:379-388.
15. Hoppe LE, Kettle R, Eisenhut M, Abubakar I, Guideline Development Group. Tuberculosis diagnosis, management, prevention, and control. Summary of updated NICE guidance. J R Soc Med 2016; 352:64747. doi:10.1136/ bmj.h6477.
16. National Institute for Health and Clinical Excellence, (NG33). Tuberculosis: diagnosis and management of tuberculosis, and measures for its prevention and control. London: NICE, 2016. https://www.nice.org.uk/guidance/ng33.
17. Pinto LM, Grenier J, Schumacher SG, Denkinger CM, Steingart KR, Pai M. Immunodiagnosis of tuberculosis: state of the art. Med Princ Pract 2012;21(1):4-13.
18. European Center for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. Stockholm, 2011. http://ecdc.europa.eu/en/publications/Publications/1103_GUI.IGRA.
19. European Center for Disease Prevention and Control. Tuberculosis report 2017. Geneva: WHO, 30 March 2017. 356(9235):1099-1104.
20. Arend SM, Meijgaard KEN, Boer K, de Palou EC, Soolinglen D, Ottenhoff TH, et al. Tuberculin skin testing and in vitro T cell responses to ESAT-6 and culture filtrate protein 10 after infection with Mycobacterium marium or M. kansasii. J Infect Dis 2002;186(12):1797-1807.
21. Pai M, Gokhale K, Joshi R, Dogra S, Kalsant L, Mandratta DK, et al. Mycobacterium tuberculosis infection in healthcare workers in rural India: comparison of a whole-blood interferon-gamma assay with tuberculin skin testing. JAMA 2005;293(22):2746-2755.
22. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim YS, 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;293(22):2756-2761.
23. Harada N, Nakajima Y, Higuchi K, Sekiya Y, Rothel J, Mori T. Screening for tuberculosis infection using whole-blood interferon-γ release tests among Japanese healthcare workers. Infect Control Hosp Epidemiol 2006;27(5):442-448.
24. Al Jahdali H, Alzahrani A, Alzahrani S, Abba AA, Memish ZA, Alrajhi AA, et al. Saudi guidelines for testing and treatment of latent tuberculosis infection. Ann Saudi Med. 2010;30(1):38-49.
25. Pai M, Behr M. Latent Mycobacterium tuberculosis infection and interferon-gamma release assays. Microb Spec 2016;495:379-388.
26. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, et al. Interferon-gamma release assays in the diagnosis of latent tuberculosis infection in healthcare workers in the United States. Am J Respir Crit Care Med 2014;189(1):77-87.
27. LoBreuk S, Castro KG. Is it time to replace the tuberculin skin test with a blood test? JAMA 2012; 308(3):241-242.
28. Banaei S, Gaur LR, Pai M. Interferon-gamma release assays for latent tuberculosis: what are the sources of variability? J Clin Microbiol 2016;54(4):845-850.
29. Tagmouli S, Slater M, Benedetti A, Kik SV, Banaei S, Datijan A, et al. Reproducibility of interferon gamma (FN7) release Assays. A systematic review. Ann Am Thorac Soc 2014;11(8):1267-1276.
30. Daley CL, Reves RR, Beard MA, Boyle J, Clark RB, Beele JL, et al. A summary of issues in the process of addressing variability around the cut point in serial interferon-γ release assay testing. Infect Control Hosp Epidemiol 2013;34(6):625-630.
31. Pai M. IFN-γ release assay for tuberculosis: a comparison of categorical data in medical research. Stat Methods Med Res. 1992;1(2):183-199.
32. Memish ZA. Infection control in Saudi Arabia: Meeting the challenges. Am J Inf Control. 2002;30(1):57-65.
33. Memish Z. Mecca bound: The challenged eNS ahead. J Travel Med 2002;9:202-206.
34. Al Jahdali H, Ahmed AE, Balkhy HH, Baharoon S, Al HejaifiiFF, Hajeer A, et al. Comparison of the tuberculin skin test and QuantiFERON-TB Gold In-Tube (QFT-G) test for the diagnosis of latent tuberculosis infection in dialysis patients. J Infect Public Health 2013;6(3):166-72.
35. Hasan HA, Shorman M, Housawi AR, Elsamamky MY. Detecting latent tuberculosis infection prior to kidney transplantation in a tertiary hospital in Saudi Arabia: comparison of the T-SPOT, TB test and tuberculin test. Br Microbiol Res J 2013;3(6):116-27.
36. Edathodu J, Varghese B, Alrajhi AA, Shoukri M, Nazmi A, Elgaml H, et al. Diagnostic potential of interferon-gamma release assay to detect latent tuberculosis infection in kidney transplant recipients. Transplant Infect Dis. 2017;19(2):e12675.
37. Abbas MA, AlHamdan NA, Fila LA, AlEnezy AK, AlQahtani MS. Prevalence of latent TB among healthcare workers in four major tertiary care hospitals in Riyadh, Saudi Arabia. J Egypt Public Health Assoc 2010; 85(1-2):61-71.
38. Menzies R, Vissandjee B. Effect of bacille Calmette-Guérin vaccination on tuberculin reactivity. Am Rev Respir Dis 1992;145(3):621-625.
39. Pereira SM, Barreto ML, Pilger D, Ro-o DR, LC. Effectiveness of first BCG vaccination against tuberculosis in school-age children without previous tuberculin test (BCG-REVAC trial): a randomised controlled trial. Lancet Infect Dis 2012;12:300-306.
40. Kang YA, Lee HW, Yoon HI, Cho B, Han SK, Shim YS, 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;293(22):2756-2761.
41. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, et al. Interferon-gamma release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. Am J Respir Crit Care Med 2014;189(1):77-87.