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Role of QuantiFERON-TB Gold In-Tube test in detection of latent tuberculosis infection in health care contacts in Alexandria, Egypt

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Tuberculosis infection represents a global health problem and a great risk to health care workers. The detection and treatment of latent tuberculosis infection is a key strategy in the control of tuberculosis. The aim of this study was to estimate the usefulness of QuantiFERON-TB Gold In-Tube test which is an interferon-gamma release assay for the detection of latent tuberculosis infection, in a group of Egyptian Health Care Workers in comparison to the tuberculin skin test. A total of 100 Health Care Workers were enrolled. Subjects diagnosed as latent tuberculosis infection by tuberculin were 88% as compared to 36% by quantiferon. Higher tuberculin positive results were associated with direct contact to tuberculosis patients and job categories as physicians and nurses, while higher quantiferon positive results were associated with longer duration of employment and absence of BCG vaccination. The overall agreement between the two tests was poor (k=0.109). The negative discordant results (quantiferon negative/tuberculin positive) were 53% and were found among both contacts and non contact group, which could reflect high number of false positive tuberculin skin test. These data suggest that using IFN-γ method to screen new entrant health care workers for latent tuberculosis infection in our population could be more helpful because it is more specific for detecting latent tuberculosis infection compared to tuberculin skin test.

Key words: Tuberculin, gamma-interferon, health care, latent infection.

INTRODUCTION

Occupational latent tuberculosis infection (LTBI) among health care workers (HCWs) is an important public health issue (Adachi et al., 2013). HCW is anyone working in a healthcare setting, regardless of direct patient TB contact (Dorman et al., 2014). Recent systematic analysis showed that the risk for tuberculosis (TB) among HCWs is consistently higher than the risk among the general population worldwide, irrespective of TB incidence in each country, and confirmed that TB is an occupational disease (Baussano et al., 2011).

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TB prevalence rate in Egypt was estimated in the World Health Organization (WHO) global report (2013) to be 29 per 100,000 populations. TB transmission in healthcare facilities can be significantly reduced with the implementation of effective TB infection control measures. While most high income countries have successfully implemented TB infection control measures, TB infection control measures are limited or virtually non-existent in most resource-limited countries (Whitaker et al., 2013).

Most high-income countries screen HCWs periodically for LTBI as part of their TB infection control programs (Whitaker et al., 2013), in an effort to identify new infections that can be targeted for preventive therapy (Zwerling et al., 2012a), but this practice is unusual in most low and middle-income countries (Whitaker et al., 2013).

Although several tests have been used to diagnose LTBI, yet till now there is no gold-standard test for the diagnosis (Dheda et al., 2005; Francis et al., 2007; Pai et al., 2007). Traditionally TB screening in HCWs has been conducted using the Tuberculin Skin Test (TST), a test with known limitations. Recently, Interferon gamma release assays (IGRAs) are being increasingly used for LTBI screening. Two commercially available IGRAs have been approved for use: the Quanti-FERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis Inc., Valencia CA) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK). IGRAs have several advantages over the TST: they require only one visit, are not affected by BCG vaccination, have less cross-reaction with non-tuberculous mycobacteria, are less subjective in measuring results, and can be repeated without boosting (Whitaker et al., 2013). In comparison with TST, the IGRA reduces the number of x-rays and the amount of chemoprevention needed (Nienhaus et al., 2013). Yet, some limitations have been reported such as false-negative or indeterminate results caused by incorrect blood sampling, improper handling of the specimen which may limit exposure of lymphocytes to the presenting antigen, or specimen obtained prior to the development of cellular immune response. Moreover, heterophile antibodies formed during other inflammatory conditions may interfere with specific responses to ESAT-6, CFP-10, or TB7.7 (p4) peptides (Mazurek et al., 2005).

Several systematic reviews have suggested that IGRAs are as sensitive, and as more specific than the TST in identifying LTBI, particularly in low TB incidence settings (Zwerling et al., 2012a). However, in high-incidence settings, there were no consistent differences in the prevalence of positive tests (Zwerling et al., 2012b). A WHO policy statement on the use of IGRA in low- and middle-income countries indicates that “data on serial testing and reproducibility of IGRAs, as well as evidence on the predictive value of IGRAs in HCWs, are still absent for high – incidence settings” (WHO, 2011).

Although the comparison of TST and QFT-GIT has been shown in the literature extensively, limited data are available concerning the study of both tests among HCWs population in Egypt (medium/high TB setting). The aim of the present study was to evaluate the usefulness of the QFT-GIT test for detecting LTBI among a group of Egyptian HCWs, in comparison to the TST.

MATERIALS AND METHODS

This study was carried out over a 3 month period from June through August 2010, and it consisted of 2 groups: 80 HCWs, selected from employees in EL-Maamora Chest Hospital TB departments, who had a close contact to sputum smear positive pulmonary TB patients for at least 3 months duration (contact group) (Morsy et al., 1997), and 20 non-exposed individuals from staff working in administrative sections that have no contact with TB patients, at Alexandria Main University Hospital (AMUH) as a control group. An informed consent was taken from all participants in the study. First, 3 ml blood was collected from each HCW for the QFT-GIT test, which was performed at the microbiology laboratory department at AMUH. Next, TST was performed for all HCWs at their work place. The study was approved by the ethics committee of AMUH.

HCWs completed a questionnaire covering demographic data, occupational and non-occupational TB exposure in the occupational environment and the duration of contact with TB patients, BCG vaccination status, history of former active TB infection, previous treatment for TB, results of previous TST, work history in the health care institution, potential non-occupational exposure to TB. BCG vaccination status is verified by scars.

Tuberculin skin test (TST)

The TST was performed using the Mantoux method by a trained nurse according to manufacturer instructions; 5TU (0.1) ml of Tuberculin PPD (Vacsera, Giza, Egypt) were injected intradermally into the inner aspect of the forearm. Correct injection was indicated by producing a palpable elevation of the skin (wheel) 6-10 mm in diameter. The test was read 48-72 h. Interpretation of the results was done according to American Thoracic Society guidelines (2000), positive test is indicated by the presence of palpable induration of 10 mm or more.

QuantiFERON®-TB Gold In-Tube test (QFT-GIT)

The QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis Ltd/Qiagen, Carnegie, Australia) was performed as per the manufacturer’s instructions. The system uses two specialized blood collection tubes; one of them contains antigens representing certain M. tuberculosis proteins ESAT- 6, CFP-10, and TB-7.7 (p4) as well as negative (Nil) controls. One mL of blood by venipuncture was introduced directly into each of the collection tubes. The tubes were vigorously shacked for 5 seconds (or 10 times) till frothing to ensure that the entire inner surface of the tube has been coated with blood. The tubes were incubated at 37ºC incubator as soon as possible, and within 16 h of collection. Incubation of the blood occurs in the tubes for 16 to 24 h, after which plasma is harvested by centrifugation and tested for the presence of IFN-y by enzyme-linked immunosorbent assay (ELISA) .The Optical Density (OD) of each well was measured within 1hour of stopping the reaction using a microplate reader fitted with a 450 nm filter and with a 620 to 650 nm reference filter. The cut-off value for positive results was ≥0.35 IU/ml. version 20. Categorical variables were described using frequencies and percentages. Chi square, Fisher’s exact; McNemar and Monte Carlo tests were used for testing associations between categorical variables. Agreement test; reported as a kappa statistic, was used as a quantitative measure of the strength of agreement between tests, where K < 0.20 (poor agreement), K = 0.21 - 0.40 (fair agreement), K = 0.41 - 0.60 (moderate agreement), K = 0.61 -

Table 1. Participant characteristics (n=100).

Characteristic	n (%)
Gender	
Male	14(14)
Female	86(86)
Age	
20- 29	35(35)
30-39	28(28)
≥ 40	37(37)
Occupation	
Nurses	64(64)
Clinician	21(21)
Worker (housekeeping)	8(8)
Lab Technician	7(7)
BCG Vaccination	
Yes	83(83)
No	17(17)
Direct Contact of TB Patients	
Yes	80(80)
No	20(20)
Duration of Work (years)	
≤ 1	4(4)
2-5	28(28)
6-9	23(23)
≥ 10	45(45)

0.80 (good agreement), *K*=0.81 - 1.00 (very good agreement). P value of kappa was also reported. Non-parametric statistical tests of significance were applied to ranks; Mann-Whitney test was used to compare two independent groups. Statistical significance was accepted as p <.05. All applied statistical tests of significance were two-tailed.

RESULTS

Participant demographics

Participant characteristics are displayed in Table 1. The mean age of the participants was 36.56 ± 9.58 yrs. The majority was females (86%) and a history of BCG vaccination was recorded in 83% of the participants. 64% of the study population were nurses, 21% clinicians 7% technicians and 8% housekeepers. 80% of the participants had direct contact with TB patients, with mean length of employment duration as a HCW in the institution was 10.55 ± 7.69 yrs.

Diagnostic tests for latent TB

As shown in Table 2, a total of 88 HCWs had a positive TST using a cut off ≥ 10 mm induration. In univariate analysis, working as a nurse and direct exposure to infectious TB patients were significantly associated with having a positive TST result. Female gender, age > 40 years, BCG vaccination and duration of employment in HCW institution ≥ 10 years were associated with higher percentage of TST positivity, but the differences were statistically non significant.

The prevalence of LTBI among the 100 participants, assessed by QFT-GIT was 36% and it correlated with the absence of BCG vaccination (58.8%) *(p*= 0.03) and a duration of employment as HCW ≥ 10 years (48.9%) (*p* = 0.014). No statistically significant association was observed for gender, age, job category and direct exposure to TB patients, despite higher rates of QFT-GIT positivity among males, working as clinician or nurse and age ≥ 40 years.

Test concordance and discordance

Table 3 shows that the concordant results (46%), predominantly positive (35%), were significantly associated with clinicians (*MCp*= 0.014). The discordant results were observed in 54 HCWs, most of them (53%) had positive TST/ negative QFT-GIT combination, which was significantly associated with nurse occupation *(MCp*= 0.014).

Concordant and discordant results were not significantly associated with age, gender, previous BCG vaccination, direct contact with TB patients and duration of exposure to TB patients (P>0.05). Positive concordant results increased among males, age ≥ 40 years, absence of BCG vaccination, duration of employment in HC institution ≥ 10 years, while most females, HCWs younger than 30 years, history of BCG vaccination, direct contact with TB patients showed higher rates of negative discordant results.

Test agreement

Table 4 shows a significant poor overall agreement between both tests among all HCWs (Kappa = 0.109, p = 0.033, 95% CI = 0.023, 0.195). Among BCG vaccinated HCWs, significant poor agreement was also observed. (Kappa = 0.105, p = 0.032, 95% CI = 0.032, 0.178). Concordance and discordance between results of both tests were not statistically significant among the 17 non BCG vaccinated HCWs. Among the 80 contacts HCWs, TST results were constantly positive, so no statistics could be computed. Also, it was observed that high negative discordant results (QFT-/TST+) were observed among both contact and control groups (57.5% and 35% respectively).

The limitations of this study: 1. Low number of patients. 2. Lack of a gold standard for LTBI. 3. Cross-sectional design with no longitudinal follow up. 4. There is a possibility that some people, who do not describe an exposure to patients with TB, may have an inadvertent exposure.

Table 2. Results of univariate analyses of potential risk factors for detection of LTBI by means of TST and QFT-GIT among the 100 HCWs

Characteristic	N (100)	TST		Test statistic (P value)	QFT-GIT		Test statistic (P value)
		Positive n (%)	Negative n (%)		Positive n (%)	Negative n (%)	
Gender							
Male	14	11 (78.6)	3 (21.4)	***(FEp***= 0.367)	8 (57.1)	6 (42.9)	***χ2***= 3.158
Female	86	77 (89.5)	9 (10.5)		28 (32.6)	58 (67.4)	(0.076)
Age							
20-29	35	32 (91.4)	3 (8.6)	***Z***= 0.265	9 (25.7)	26 (74.3)	***Z***= 1.779
30-39	28	23 (82.1)	5 (17.9)	(0.791)	10 (35.7)	18 (64.3)	(0.075)
≥ 40	37	33 (89.2)	4 (10.8)		17 (45.9)	20 (54.1)	
Occupation*							
Nurse	64	64 (100)	0 (0)		22 (34.4)	42 (65.6)	
Clinician	21	17 (81)	4 (19)	***MCp*** <0.001	11 (52.4)	10 (47.6)	***(MCp*** = 0.244)
Worker (housekeeping)	8	5 (62.5)	3 (37.5)		2 (25)	6 (75)	
Lab Technician	7	2 (28.6)	5 (71.4)		1 (14.3)	6 (85.7)	
BCG Vaccination							
Yes	83	74 (89.2)	9 (10.8)	***(FEp***=*0.*424)	26 (31.3)	57 (68.7)	***χ2***= 4.631
No	17	14 (82.4)	3 (17.6)		10 (58.8)	7 (41.2)	(0.031)
Direct Contact with TB patients							
Yes	80	80 (100)	0 (0)	***(FEp*** <0.001)	34 (42.5)	46 (57.5)	**χ2**= 7.335
No	20	8 (40)	12(60)		2 (10)	18 (90)	(0.077)
Duration of Work (years)							
≤ 1	4	4 (100)	0 (0)	***Z***=1.752	1 (25)	3 (75)	***Z***= 2.453
2-5	28	21 (75)	7 (25)	(0.080)	6 (21.4)	22 (78.6)	(0.014)
6-9	23	21 (91.3)	2 (8.7)		7 (30.4)	16 (69.6)	
≥ 10	45	42 (93.3)	3 (6.7)		22 (48.9)	23 (51.1)	

Table 3. Distribution of the concordant and discordant results for QFT-GIT and TST tests.

Characteristic	N	Concordant (n = 46)		Discordant (n = 54)		*Test statistic (P value)*
		Neg/Neg (n=11) n (%)	Pos/Pos (n=35) n (%)	Pos[a]/Neg (n=1) n (%)	Neg[b]/Pos (n=53) n (%)	
Gender						
Male	14	2 (14.2)	7 (50)	1 (7.14)	4 (28.5)	***χ2***= 2.191
Female	86	9 (10.5)	28 (32.5)	0 (0)	49 (56.9)	(0.139)
Age						
20-29	35	3 (8.57)	9 (25.7)	0 (0)	23 (67.7)	***Z***= 1.423
30-39	28	5 (17.8)	10 (35.7)	0 (0)	13 (46.4)	(0.155)
≥40	37	3 (8.1)	16 (43.2)	1 (2.7)	17 (45.9)	
20-29	35	3 (8.57)	9 (25.7)	0 (0)	23 (67.7)	***Z***= 1.423
30-39	28	5 (17.8)	10 (35.7)	0 (0)	13 (46.4)	(0.155)
≥40	37	3 (8.1)	16 (43.2)	1 (2.7)	17 (45.9)	

Table 3. Contd.

Occupation						
Nurses	64	0 (0)	22 (34.4)	0 (0)	42 (65.6)	
Clinician	21	4 (19.1)	11 (52.4)	0 (0)	6 (28.6)	(***MCp***= 0.014)
Worker (housekeeping)	8	3 (37.5)	2 (25)	0 (0)	3 (37.5)	
Lab Technician	7	4 (57.1)	0 (0)	1 (14.3)	2 (28.6)	
BCG Vaccination						
Yes	83	9 (10.8)	26 (31.3)	0 (0)	48 (57.8)	***χ2***=2.885
No	17	2 (11.8)	9 (52.9)	1 (5.9)	5 (29.4)	(0.089)
Direct Contact of TB Patients						
Yes	80	0 (0)	34 (42.5)	0 (0)	46 (57.5)	***χ2***=1.973
No	20	11 (55)	1 (5)	1 (5)	7 (35)	(0.160)
Duration of Work (years)						
≤ 1	4	0 (0)	1 (25)	0 (0)	3 (75)	
1-5	28	7(25)	6 (21.4)	0 (0)	15 (53.6)	***Z***= 0.813
6-9	23	2 (8.7)	7 (30.4)	0 (0)	14 (60.9)	(0.416)
≥ 10	45	2 (4.4)	21(46.7)	1 (2.2)	21 (46.7)	
≤ 1	4	0 (0)	1 (25)	0 (0)	3 (75)	***Z***= 0.813 (0.416)
1-5	28	7(25)	6 (21.4)	0 (0)	15 (53.6)	
6-9	23	2 (8.7)	7 (30.4)	0 (0)	14 (60.9)	
≥ 10	45	2 (4.4)	21(46.7)	1 (2.2)	21 (46.7)	

[a]Positive by QFT-GIT, [b]Negative by QFT-GIT

Table 4. Agreement and disagreement between results of QFT-GIT and TST and effect of BCG vaccination and contact with TB patients.

Parameter	N	PCR	NCR	Kappa		*p*	DR[a]	NDR[b]	McNemar
		n (%)	n (%)	Value	95% CI		n (%)	n (%)	*p*
All subjects	100	35 (35.0)	11 (11.0)	0.109	0.023, 0.195	0.033	1 (1.0)	53 (53.0)	<0.001
BCG vaccinated	83	26 (31.3)	9 (10.8)	0.105	0.032, 0.178	0.032	0 (0.0)	48 (57.8)	<0.001
Not BCG vaccinated	17	9 (52.9)	2 (11.8)	0.203	-0.213, 0.619	0.323	1 (5.9)	5 (29.4)	0.219
Contacts	80	34 (42.5)	-	-	-	-	-	46 (57.5)	-
Non- contatcts	20	1 (5.0)	11 (55.0)	0.048	-0.0269 , 0.366	0.761	1 (5.0)	7 (35.0)	0.070

PCR; positive concordance rate, NCR; negative concordance rate, PDR; positive discordance rate, NDR; negative discordance rate. [a]Positive by QFT-GIT, [b]Negative by QFT-GIT.

DISCUSSION

In our study, the proportion of LTBI assessed by TST was 88 and 36% by QFT-GIT. Close results were reported in Egypt in Abu-Taleb et al. study (2011), where 71.1% of contacts were diagnosed as latent TB infection by TST and 31% by IFN-γ assay. This discrepancy might be explained by high false positives TST results, as HCWs repeat TSTs during their employment, which may further boost their reaction to the TST. This hypothesis is supported by Kang et al. (2005) study.

Our TST results were highest rate among nurses (100%) and clinicians (81%). This was in agreement with Drobniewski et al. (2007) study, where the proportion of LTBI assessed by TST was 40.8% and was significantly higher in doctors and nurses (39.1%). Significant positive TST results were higher among our HCWs in direct contact with TB patients. This was in accordance with Mirtskhulava et al. (2008) and Machado et al.,(2009) studies, where TST results in HCWs and household contacts with TB patients were (67% and 55.6% respectively). Lower result (49.5%) was reported in the study of

Helmy et al. (2011), conducted on a population of close household TB contacts in Egypt. Even very low results were reported by other studies, such as 12.8% (Nienhaus et al., 2008a) and 7.2% (Schablon et al., 2009) in Germany. This could be explained by the low prevalence of TB in Germany in comparison with Egypt and Brazil.

In the present study, there was no statistically significant association between positive TST results and gender, age and duration of employment in the health care institution. This may be explained by the small number of the study group. The rate of detection of LTBI assessed by QFT-GIT in our study was 36%. Low detection rates by QFT-GIT as compared to TST were also reported by other scientists: Harada et al. (2006), Soborg et al. (2007), Niehaus et al.(2008a), Stebler et al. (2008) and Ringshausen et al., (2009).

But the relatively high results of positive QFT-GIT found in HCWs (36%) in this study may reflect the higher infection risk in this occupational area due to intermediate prevalence of TB in our country (29 per 100000 populations) as what was reported by Khanna et al. (2009), who stated that participants who were born in a country with a high TB prevalence, and/or who were born in Africa were significantly more likely to have a positive QFT-GIT result. Higher QFT-GIT results was reported by Helmy et al. (2011), in Egypt, being 49.5% in a population of close household TB contacts, which may be explained by the intimate closer contact between the TB patients and the close household contacts.

The small sample size in this study might explain the reported insignificant correlation between positive QFT-GIT results and occupation. Other studies investigating the risk of physicians did not indicate an increased infection risk for physicians (Schablon et al., 2009).Other researchers reported a prevalence of LTBI in nurses; a subgroup with high level of patient contact, and thus potential exposure to TB cases (Joshi et al., 2006; Yanai et al., 2003; Garcia-Garcia et al., 2001).

There was a significant positive results of QFT-GIT associated with longer duration of work (≥ 6 years). The rate of detection of LTBI assessed by QFT-GIT was significantly higher in non-BCG vaccinated than in vaccinated HCWs. This indicates that QFT-GIT is not affected by previous BCG vaccination as it utilizes M. tuberculosis specific antigens (Nienhaus et al., 2011; Andersen et al., 2000).

Our QFT-GIT positive results were higher in older age group (≥ 40 years), a finding that was supported by Ringhausen et al. (2009), which might indicate age dependency of QFT-GIT that is not observed with TST. Moreover, QFT-GIT positive results were higher among HCWs in direct contact with TB patients, as what was reported in Stebler et al. (2008) and Mirtskhulava et al. (2008) studies.

In this study, concordant results were lower than discordant results (46 and 54% of HCWs, respectively). The results of the present study were matching with Harada et al. (2006) who compared the performance of TST and Quantiferon in a total of 304 HCWs. They found that concordant results were lower than discordant results (14 and 86%, respectively).

On the other hand, the present results disagreed with the Egyptian study of Helmy et al. (2011), where concordant results were (65.5%) and discordant results (34.4%) and were not affected by gender or age. Other non matching studies: Connell et al. (2006) and Kang et al. (2005), where the concordant results were higher than the discordant results.

Positive concordant results (QFT+/TST+) increased with increasing age and increasing duration of work as HCW in this study. Joshi et al. (2006) reported that increasing age and duration of employment in health care facility (indicating longer cumulative exposure) were associated with higher prevalence of LTBI in most studies.

The QFT-/TST+ discordance increased from 29.4% in non BCG vaccinated to 57.8% in vaccinated HCWs, and most of non-vaccinated had concordant positive results. This was in accordance with Nienhaus et al. (2011) study, which reflects that TST is usually affected by previous BCG vaccination, while QFT-GIT is not affected and hence low specificity of TST in detection of LTBI in comparison with QFT-GIT.

Brock et al. (2004) compared the performance of TST and Quantiferon in a total of 45 contacts of persons having active pulmonary TB, none of them was BCG vaccinated. Concordant results were obtained in 93% of cases while in only 7% discordant results were obtained. The higher concordance here may be attributed to the absence of BCG vaccination and this confirms the concept that BCG vaccination affects greatly performance of TST. In 3 studies of Kang et al. (2005), Herada et al. (2006) and Diel et al. (2006a) discordance was greater in persons with BCG vaccination than in those who were not vaccinated.

The poor overall agreement (k= 0.109) reported between TST and QFT-GIT tests among our HCWs, may be explained by the negative discordant QFT -/ TST+ results found in more than half the subjects (53%). Poor agreement was also reported by other studies (Ringshausen et al., 2009; Vinton et al., 2009; Nienhaus et al., 2008b; Diel et al., 2006b) and all confirmed that the BCG is a major confounder of TST results. These negative discordant results were observed among both contact and non-contact group (57.5% and 35% respectively). This could reflect a high rate of false positive TST, which could be explained by exposure to non tuberculous mycobacteria (Franken et al., 2007), or the fact that the antigen used in TST (PPD) is a shared antigen present in *M. tuberculosis* complex and non-tuberculous mycobacteria (Pai et al., 2004; Menzies et al., 2007), but in QFT-GIT the antigens used are *M. tuberculosis* specific antigens therefore considered better than TST in screening of HCWs for LTBI (Brook et al., 2004).

CONCLUSION AND RECOMMENDATION

Results of LTBI detected by the TST were higher than those detected by QFT-GIT among our group of Egyptian HCWs. Higher TST positive results were associated with direct contact to TB patients and certain job categories as physicians and nurses, while higher QFT-GIT positive results were associated with longer duration of employment and absence of BCG vaccination. The poor overall agreement (k=0.109) and the high negative discordant results (QFT-/TST+) can be explained by high BCG vaccination coverage in our country. The rate of discordant results (QFT-/TST+) were found among both contacts and non contacts group, which again could reflect high number of false positive TST. Therefore, we recommend using QFT-GIT to screen new entrant HCWs for LTBI in our population because it is more specific as compared to TST. Also, QFT-GIT may provide additional information for diagnosis and strategic management of preventive treatment in BCG vaccinated HCWs, avoiding unnecessary treatment to those not really infected.

Conflict of Interests

The author(s) have not declared any conflict of interests.

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