A validity study of the QuantiFERON-TB Gold (QFT-TB) method for the diagnosis of pulmonary tuberculosis in a high risk population

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Tuberculosis (TB) is a major health problem throughout the world and represents the most frequent cause of death for a single infectious agent worldwide [1]. Timely diagnosis of active TB cases is important for TB control. Currently available methods for diagnosis of pulmonary TB include chest X-ray, microscopic examination of sputum smear, culturing of sputum samples and also assay based on proliferation of nucleic acids (polymerase chain reaction, PCR) [2]. The isolation of mycobacterium tuberculosis (MTB) takes up to 6 weeks and cultures may remain falsely negative [3]. The purified protein derivative (PPD) skin test, for detection of active TB has low sensitivity and in individuals vaccinated with Bacillus Calmette-Guerin (BCG), it is often associated with a false-positive result because of cross-reactive immune responses results to antigens common to MTB [4]. In the past decade, the identification of regions of the MTB genome missing from BCG and most non-tuberculosis mycobacterium (NTM) provided new diagnostic tools [5]. The RD1 region in the genome of MTB encodes 6 KDa early secretory antigenic target (ESAT-6) and culture filtrate protein 10 (CFP-10) that these proteins are applied as antigens to stimulate T-cells [3]. The response of T-cells to these proteins is a measurable secretion of interferon-γ (IFN-γ). On this basis, two methods (QuantiFERON-TB Gold and ELISPOT) have been developed and licensed for commercial distribution. One test, the QuantiFERON-TB Gold method (Cellestis, Victoria, Australia) uses an enzyme-linked immunosorbant assay (ELISA) to measure IFN-γ in whole blood. The other test, T-SPOT TB (Oxford Immunotec, Oxford, United Kingdom), uses the ELISPOT technique to measure peripheral blood mononuclear cells that produce IFN-γ [3, 6, 7]. After the QuantiFERON-TB Gold method was approved by FDA, and following an operational guide delivered for this test by CDC (Center for Disease Control and Prevention) as a contributory device for diagnosis of active TB and latent TB infections (LTBI), this test was routinely used in some countries [8]. At present, most research using this method has been conducted in populations with low risk of TB. However, the use of this method as a diagnostic test for active TB in societies with high risk of tuberculosis infections should be evaluated. Therefore the aim of this study was evaluation QFT-TB Gold in tube for active TB diagnosis in high risk region of Iran, Sistan and Baluchesta province. Our study was performed at the Bu-Ali hospital in Zahedan City, in southeastern Iran, on 81 persons who were clinically suspected to active TB. Here, diagnosis of active TB was performed using acid fast bacilli staining in three times, tuberculosis skin test (TST) and by observing the responding to anti-tuberculosis treatment for one week. Patients with a positive response to treatment were recommended to complete their treatments. The QFT-TB Gold in tube test was performed according to the recommendation of the manufacturer (Cellestis Ltd, Carnegie, Victoria, Australia), and data were analysed by SPSS (15) and SISA (2002) software as well as Cellestis Inc. software from kit. Table 1 and 2 show patient characteristics and QFT-TB Gold results, respectively. To evaluate QFT-TB Gold in tube as a diagnostic test, we calculated the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV). To estimate sensitivity, active TB was considered to be confirmed in people who responded to treatment. This approach was used in sensitivity studies with both TST and QFT methods [9]. Our results showed a sensitivity of approximately 85% for active TB. In addition, our study showed that 77% of patients with active TB had a positive result in the QFT-TB. In a study by Dewan et al. QFT-TB sensitivity on patients suspected of having active TB was given at 62%. They showed that 64% of patients with active TB have a positive result for QFT-TB [10]. Another study by Pernille et al on patients with suspected active TB showed 85% sensitivity for active TB in the QFT-RD1 test [11]. The studies completed thus far, estimated the sensitivity of QFT-TB test lie between 62-95% [12]. Our result seems to confirm these findings and is comparable with them. In our study, the specificity of QFT-TB Gold in tube was calculated about 53.2%, whereas the previous studies showing the specificity of 85-95%. One of the reasons for low specificity of this study and potential limitation of QFT-TB as well as other tests, is that they are based on immunological reaction that can not distinguish between LTBI and active TB. In view of these observations, if the target population in studies of persons with suspected to pulmonary TB lives in a region with a high risk for TB infection, a reduced specificity of this test is to be expected. In Pernille's study, the specificity of QFT-TB was estimated 60% for active TB diagnosis. They also analysed tuberculosis risk factors in non-TB patients with positive QFT-TB results and found 80% of them to have risk factors suggestive of LTBI [11].

Our study showed that 92% of patients with at least one pathological sputum smear had a positive QFT-TB Gold. The previous studies have shown that 85% patients with a positive smear have positive results for RD1 antigens [13]. In this study, the positive and

Table 1

Characteristics of patients suspected of having pulmonary tuberculosis.

Variable	Subject n (%)
Age (years ± SD)	51.9 ± 14.9
Gender	
male	26 (32.1)
female	55 (67.9)
Vaccination	
done	24 (36.5)
not done	41 (63.5)
Active tuberculosis	31 (35.2)
Without tuberculosis	
Asthma	2 (2.3)
Pneumonia or bronchitis	38 (43.2)
Other disease	17 (19.3)

Table 2

QFT-TB Gold result in comparison with responding of treatment.

QFT-TB result	Final diagnosis		
	TB	Not TB	Total
Positive	24	22	46
Negative	4	25	29
Indeterminate	3	3	6
Total	31	50	81

Table 3

Diagnostic confidence for QFT-TB and TST.

Index experiment	PPV %	NPV %	LR+	LR–	Odds ratio
QFT-TB	52	86	1.83	0.27	6.8
TST	54	67	1.04	0.97	1.07

negative predictive value (PPV, NPV) were assayed for QFT-TB Gold as a diagnostic test (table 3). We used tuberculin skin test (TST) (only 65 of 81 results were available) to compare with QFT-TB Gold test, since both involve an immune response. In conclusion, our study confirms results of other studies applying this method for diagnosis of active TB. Although the QFT-TB Gold showed high sensitivity and specificity in low-risk populations, in such populations it may be useful for the diagnosis of both LTBI and active TB, without the need for other tests. However, in high incidence regions, we think it should be used as a supplementary tool for diagnosis of active TB together other diagnostic test as CDC suggests in its Guidelines.

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