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Comparison of Two Commercially Available Gamma Interferon Blood Tests for Immunodiagnosis of Tuberculosis▽

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We evaluated the T-SPOT.TB and Quantiferon-TB Gold *In tube* (QFN-G-IT) tests for diagnosing *Mycobacterium tuberculosis* infection. T-SPOT.TB was more sensitive than QFN-G-IT in diagnosing both active and latent infection. Both gamma interferon tests were unaffected by prior *Mycobacterium bovis* BCG vaccination. Among children who were not BCG vaccinated but had a positive tuberculin skin test, QFN-G-IT was negative in 53.3% of cases, and T-SPOT.TB was negative in 50% of cases.

The tuberculin skin test (TST) is used for diagnosing latent *Mycobacterium tuberculosis* infection (LTBI) (11). The biggest drawback of TST is the cross-reaction with nontuberculous mycobacteria (NTM) or with *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) vaccine strains (10). The 6-kDa *Mycobacterium tuberculosis* protein early secreted antigenic target 6 (ESAT-6) and the 10-kDa culture filtrate protein (CFP-10), encoded in the region of deletion 1 (RD1), have been described as being present in *M. tuberculosis* but not in any BCG strain or the majority of NTM strains (1).

In vitro assays for measuring gamma interferon (IFN-γ) released by T cells after RD1 antigen stimulation have been developed (7, 14, 18, 19). On the basis of this technology, the following three commercial IFN-γ tests are available: Quantiferon-TB Gold assay (QFN-Gold), Quantiferon-TB Gold *In tube* assay (QFN-G-IT; Cellestis Limited, Carnegie, Victoria, Australia), and T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom). The main differences between QFN-Gold and QFN-G-IT are that, in the latter, antigens are included together in the same blood sample collection tube and, in addition, a third stimulating antigen, TB7.7 (Rv2654), is included (4). This new antigen is encoded in RD11 and is lacking in the BCG strains as well as in most common NTM strains (4).

The aim of this study was to assess the ability of the new QFN-G-IT and T-SPOT.TB tests to diagnose *M. tuberculosis* infection in clinical practice, comparing the results with those of TST.

Study population. We prospectively recruited 626 individuals between September 2004 and November 2006 who attended the Hospital Universitari Germans Trias i Pujol or the TB Control and Prevention Unit of Barcelona for ongoing studies of active TB or LTBI. We classified the adults and children enrolled in the study into the following three groups of patients: patients with etiological diagnosis of active TB at the beginning of the treatment, individuals enrolled during a contact tracing study as close contacts of patients with active pulmonary TB, and individuals studied for screening of latent TB. The main demographic characteristics of the study population are shown in Table 1. Ethics approval for this study was provided by the corresponding ethics committees.

After obtaining written informed consent from all enrolled persons, a detailed questionnaire about the possible risk factors of exposure to *M. tuberculosis* was completed by each patient. Subjects were also asked to indicate the results of any previous TST, whether they had received BCG vaccination, details of any contact with a person who had TB, any risk factors associated with human immunodeficiency virus infection, and whether they had any other medical conditions. Data were also collected from medical records of chest radiography, along with the results and dates of culture. In our study, only participants with BCG scars were considered BCG vaccinated.

TST. Two tuberculin units of purified protein derivative RT23 (Statens Serum Institut, Copenhagen, Denmark) was administered by the Mantoux method. Induration was measured after 72 h. Indurations of 5 mm or greater were considered positive (20). All purified protein derivative stimuli were placed and read by certified members of the staff who regularly perform these duties.

T-SPOT.TB. T-SPOT.TB assays were performed as described previously, using 35 overlapping peptides spanning the lengths of ESAT-6 and CFP-10 (15). The test and the interpretation of the results were performed following the manufacturer's instructions. The presence of reactive antigen-specific T cells was revealed as a spot on the well. Spots were scored manually in all cases, and in some borderline cases, scores were also obtained with the aid of an automated AID enzyme-linked immunospot assay plate reader (AID Systems, Strassberg, Germany).

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TABLE 1. Demographic characteristics and clinical details for patients in this study[b]

Variable	No. (%) of adults in group			No. (%) of children in group		
	Patients with active TB (n = 33)	Contact tracing study (n = 206)	Screening for LTBI[a] (n = 253)	Patients with active TB (n = 9)	Contact tracing study (n = 64)	Screening for LTBI[a] (n = 61)
Gender						
Female	11 (33.3)	121 (58.7)	101 (39.9)	2 (22.2)	37 (57.8)	32 (52.5)
Male	22 (66.7)	85 (41.3)	152 (66.1)	7 (77.8)	27 (42.2)	29 (47.5)
Age						
<5 yr				3 (33.3)	9 (14.1)	3 (4.9)
5–18 yr				6 (66.7)	55 (85.9)	58 (95.1)
18–35 yr	23 (69.7)	136 (66)	138 (54.5)			
35–75 yr	8 (24.2)	59 (28.6)	115 (45.4)			
>75 yr	2 (6.1)	11 (5.4)	0 (0)			
BCG vaccination						
Yes	9 (27.3)	82 (39.8)	97 (38.3)	1 (11.1)	46 (71.9)	39 (63.9)
No	24 (72.7)	124 (60.2)	156 (61.7)	8 (88.9)	18 (28.1)	22 (36.1)
Immunosuppression status						
AIDS patients	0 (0)	0 (0)	19 (7.5)	0 (0)	0 (0)	0 (0)
Treatment with systemic steroids	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Cancer chemotherapy	0 (0)	1 (0.5)	3 (1.2)	0 (0)	0 (0)	0 (0)
None	33 (100)	205 (99.5)	229 (90.5)	9 (100)	64 (100)	61 (100)
Country of birth						
Immigrants from countries with high prevalence of TB	17 (51.5)	97 (47.1)	82 (32.4)	2 (12.5)	45 (69.8)	42 (68.9)
Autochthon Spanish population	16 (48.5)	109 (52.9)	171 (67.6)	7 (87.5)	19 (30.2)	19 (31.1)

[a] Conducted on recent immigrants from countries with a high prevalence of TB, the homeless, or school teachers enrolled during preemployment examinations.
[b] There were a total of 626 participants in the study.

QFN-G-IT. Pools of overlapping peptides representing ESAT-6, CFP-10, and TB7.7 were used as TB-specific antigens in the whole-blood IFN-γ assay. The test and the interpretation results were performed according to the manufacturer's instructions.

Statistical methods. Concordance between the tests was assessed using Cohen's kappa coefficient. We used the McNemar test to compare the proportions of indeterminate, negative, and positive results among the QFN-G-IT, T-SPOT.TB, and TST assays. The differences in function of vaccination and immunosuppression status were calculated using the nonparametric Mann-Whitney U test. Differences were considered significant when the P value was <0.05. All analyses were done with SPSS statistical software for Windows (SPSS, version 14.0; SPSS Inc., Chicago, IL).

Positive T-SPOT.TB results were obtained for 44.7% (280/

TABLE 2. T-SPOT.TB, QFN-G-IT, and TST results for different groups in adult and child populations

Test and result	No. (%) of adults in group				No. (%) of children in group			
	Overall (n = 492)	Patients with active TB (n = 33)	Contact tracing study (n = 206)	Screening for LTBI (n = 253)	Overall (n = 134)	Patients with active TB (n = 9)	Contact tracing study (n = 64)	Screening for LTBI (n = 61)
T-SPOT.TB								
Positive	229 (46.6)	30 (90.1)	90 (43.7)	109 (43.1)	51 (38.1)	6 (66.7)	32 (62.7)	13 (21.3)
Negative	259 (52.6)	2 (6.1)	114 (55.3)	143 (56.5)	80 (59.7)	1 (11.1)	31 (48.4)	48 (78.7)
Indeterminate	4 (0.8)	1 (3)	2 (1)	1 (0.4)	3 (2.2)	2 (22.2)	1 (0.7)	0 (0)
QFN-G-IT								
Positive	192 (39)	27 (81.8)	70 (33.9)	95 (37.5)	50 (37.3)	6 (66.7)	28 (43.8)	16 (26.2)
Negative	299 (60.8)	6 (18.2)	135 (65.6)	158 (62.5)	84 (62.7)	3 (33.3)	36 (56.3)	45 (73.8)
Indeterminate	1 (0.2)	0 (0)	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TST								
Positive	366 (74.4)	31 (93.9)	150 (72.8)	185 (73.1)	115 (85.8)	9 (100)	53 (82.8)	53 (86.9)
Negative	126 (25.6)	2 (6.1)	56 (27.2)	68 (26.9)	19 (14.2)	0 (0)	11 (17.2)	8 (13.1)
Indeterminate	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TABLE 3. T-SPOT.TB, QFN-G-IT, and TST positive results in diagnosing LTBI regarding BCG vaccination status

Diagnostic test	No. (%) of positive results			
	Contact tracing studies		Screening for LTBI	
	Non-BCG-vaccinated subjects (n = 142)	BCG-vaccinated subjects (n = 128)	Non-BCG-vaccinated subjects (n = 178)	BCG-vaccinated subjects (n = 136)
T-SPOT.TB	67 (47.2)	55 (43)	73 (41)	49 (36)
QFN-G-IT	57 (40.1)	41 (32)	65 (36.5)	46 (33.8)
TST	89 (62.7)	114 (89.1)	121 (68)	117 (86)

626 patients) of all individuals studied, compared with 38.7% for QFN-G-IT (242/626 patients). T-SPOT.TB produced significantly more positive results than did QFN-G-IT ($P < 0.001$). TST was positive in 76.8% of cases. The number of positive results obtained by TST was significantly higher than those obtained by both IFN-γ tests ($P < 0.001$). The agreement between QFN-G-IT and T-SPOT.TB was 83.2% (521/626 samples) (κ = 0.66; standard error, 0.029). The overall agreement between T-SPOT.TB and TST was 64.5% (404/626 samples) (κ = 0.34; standard error, 0.029), and that between QFN-G-IT and TST was 58.1% (κ = 0.26; standard error, 0.026). In Table 2, we show the results of the tests for the different groups of patients (divided between adults and children).

Regarding BCG vaccination status, the overall differences between the results for vaccinated and nonvaccinated subjects were significant for TST ($P < 0.001$) and not significant for QFN-G-IT ($P = 0.174$) and T-SPOT.TB ($P = 0.332$). The number of positive results for each group of patients and the agreement between the tests are shown in Tables 3 and 4.

For pediatric patients, the overall agreement between both IFN-γ tests for patients diagnosed with active TB was 77.8% (7/9 patients) (κ = 0.71; standard error, 0.256) (Table 2). The overall rate of positive results for patients studied for LTBI was 36% (45/125 patients) for T-SPOT.TB, 35.2% (44/125 patients) for QFN-G-IT, and 84.8% (105/125 patients) for TST. However, the agreement rates between T-SPOT.TB and TST for nonvaccinated and BCG-vaccinated patients enrolled for LTBI diagnosis were 62.5% (25/40 patients) (κ = 0.33; standard error, 0.101) and 46.4% (39/85 patients) (κ = 0.12; standard error, 0.043), respectively; those between QFN-G-IT and TST were 57.5% (23/40 patients) (κ = 0.24; standard error, 0.101) and 42.3% (36/85 patients) (κ = 0.08; standard error, 0.044), respectively; and those between T-SPOT.TB and QFN-G-IT were 90% (36/40 patients) (κ = 0.79; standard error, 0.106) and 84.7% (72/85 patients) (κ = 0.68; standard error, 0.84), respectively. The differences in results regarding BCG vaccination were significant for TST ($P = 0.037$) and nonsignificant for T-SPOT.TB ($P = 0.752$) and QFN-G-IT ($P = 0.713$).

In our study, we found few indeterminate results; in seven cases (1.1%), the T-SPOT.TB result was indeterminate, and in another one (0.2%), the QFN-G-IT result was indeterminate (Tables 2 and 3). In our study, the indeterminate results were not obtained for immunosuppressed patients. Among the 25 immunosuppressed patients, the T-SPOT.TB assay was positive in 6 cases, the QFN-G-IT assay was positive in 8 cases, and TST was positive in 12 cases. The agreement between T-SPOT.TB and QFN-G-IT for immunosuppressed patients was 76% (19/25 patients) (κ = 0.41; standard error, 0.198).

In the last year, few studies have been published comparing T-SPOT.TB and QFN-Gold (2, 8, 12, 16). Lee et al. (16) compared T-SPOT.TB and QFN-Gold for 218 subjects (87 people with active TB and 131 people at low risk of TB). They found that T-SPOT.TB was the more sensitive test (95.4%). Kang et al. (12) found that the sensitivities for diagnosing active TB of QFN-Gold and T-SPOT.TB were 89% and 92%, respectively. In our experience, T-SPOT.TB was also a more sensitive test than QFN-G-IT.

Ferrara et al. (8) evaluated the T-SPOT.TB and QFN-Gold tests in a prospective study that enrolled 393 patients who were studied for suspected latent or active TB. They detected more indeterminate results with QFN-Gold than with T-SPOT.TB, and the indeterminate results were associated with immunosuppressive treatments for both tests. In contrast, we did not find indeterminate results to be associated with immunosuppression status. The population studied by Ferrara et al. in-

TABLE 4. Concordance and agreement (Cohen's κ coefficient) between TST, T-SPOT.TB, and QFN-G-IT results for different groups of patients

Patient group	TST vs T-SPOT.TB		TST vs QFN-G-IT		T-SPOT.TB vs QFN-G-IT	
	Concordance[a] (%)	κ (SE)	Concordance[a] (%)	κ (SE)	Concordance[a] (%)	κ (SE)
Patients with active TB	36/42 (85.7)	0.30 (0.237)	34/42 (81)	0.28 (0.159)	34/40 (85)	0.49 (0.173)
Contact tracing study						
Non-BCG-vaccinated subjects	110/142 (77.5)	0.58 (0.066)	100/142 (70.4)	0.44 (0.066)	120/142 (84.5)	0.71 (0.050)
BCG-vaccinated subjects	67/128 (52.3)	0.14 (0.046)	51/128 (39.8)	0.06 (0.036)	98/128 (76.6)	0.52 (0.073)
Overall	177/270 (65.6)	0.35 (0.046)	151/270 (55.9)	0.29 (0.040)	218/270 (80.7)	0.61 (0.047)
Screening for LTBI						
Non-BCG-vaccinated subjects	127/178 (71.3)	0.47 (0.055)	118/178 (66.3)	0.39 (0.053)	153/178 (86)	0.72 (0.054)
BCG-vaccinated subjects	64/136 (47.1)	0.12 (0.042)	61/136 (44.9)	0.11 (0.040)	117/136 (86)	0.69 (0.065)
Overall	191/314 (60.8)	0.30 (0.037)	179/314 (57)	0.25 (0.035)	270/314 (86)	0.71 (0.041)

[a] No. of patients with concordant results/total no. of patients.

cluded many immunosuppressed patients (38%), as opposed to our study, where the immunosuppressed population reached only 3.9%.

Finally, Arend et al. (2) compared the T-SPOT.TB and QFN-G-IT tests for 785 non-BCG-vaccinated adult subjects in a contact tracing study. They obtained an interassay agreement of 89.6% ($\kappa = 0.59$). In our experience, the agreement between both IFN-γ tests for non-BCG-vaccinated adults involved in contact tracing studies was also very high (84.5%; $\kappa = 0.71$).

Very few studies have been conducted on the pediatric population (5–7). Connell et al. (5) compared QFN-Gold and TST for detecting LTBI and found a low agreement between both techniques ($\kappa = 0.3$), with the IFN-γ test being negative for 70% of the 37 children with a positive TST. In our study, the agreement between the IFN-γ tests and the TST was also very low. In our experience, among children not vaccinated with BCG, QFN-G-IT was negative for 53.3% of children with a positive TST, and T-SPOT.TB was negative in 50% of cases. The percentage of positive TST results among pediatric patients as a consequence of NTM infection, as described previously, is not negligible (3). The utilization of IFN-γ tests could reduce the false diagnosis of *M. tuberculosis* infection in children with NTM infection (6).

Although further research in certain areas is required to fully elucidate the real role of IFN-γ tests in the management of *M. tuberculosis* infection (9, 13, 17), our results show enough evidence to state that IFN-γ tests are less affected by BCG vaccination than is TST and could avoid unnecessary latent tuberculosis treatment among adult and child populations.

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