Comparison of Mantoux and QuantiFERON TB Gold Tests for Diagnosis of Latent Tuberculosis Infection in Army Personnel

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The tuberculin skin test (TST) was compared with QuantiFERON-TB Gold in-tube (QFT-GIT) test for the diagnosis of tuberculosis in non-Mycobacterium bovis BCG-vaccinated military personnel. Among subjects positive by TST, 44.4% of recruits were positive by QFT-GIT compared with 11.5% subjects tested after missions abroad, suggesting that most TST conversions in the latter group were caused by nontuberculous mycobacteria.

Military personnel can be sent to countries of high endemicity for tuberculosis (TB); therefore, these employees are at higher risk of TB infection. Non-Mycobacterium bovis BCG-vaccinated recruits entering the army are screened using the tuberculin skin test (TST) for the diagnosis of latent TB infection (LTBI), while BCG-vaccinated recruits are screened using chest radiography. Screening is repeated following each return from a mission. If TST conversion (TST, ≥10 mm) is documented, prophylactic isoniazide is prescribed for 6 months.

Earlier studies using skin testing with sensitins from atypical mycobacteria, such as M. avium or M. scrophulaceum, indicated that about half of the positive TST reactions in military personnel following return from missions were false positive (3). New diagnostics like QuantiFERON-TB Gold in-tube (QFT-GIT) have been developed using the TB-specific antigens ESAT-6, CFP-10, and TB7.7 (1, 7, 15). The advantages of these new assays over the TST are the higher specificities (excluding false-positive results due to BCG or environmental mycobacteria), logistic simplicity, and need of only one patient visit (9, 14, 15, 17). In this study, we used QFT-GIT for screening military personnel.

The purpose of this prospective, cross-sectional observational study was to compare the TST with QFT-GIT for the detection of TB in Dutch Armed Forces personnel. We aimed to recruit 750 employees to be screened for TB infection 6 weeks after returning from military missions in an area of TB endemicity and 150 recruits (new employees of the Dutch Armed Forces) as controls. In order to include a sufficient number of subjects with positive TST among those who had been on missions, a portion of the subjects were randomly included on the day of TST administration and a portion were included on the day of TST reading if the TST result was >0 mm. The Ethical Review Board of the Leiden University Medical Center approved the study protocol (protocol number P04-027). All participants provided written informed consent. The TST and QFT-GIT test were carried out as described previously (2). Analyses were performed using SPSS (version 12.0.1; Apache Software Foundation). Differences between the study groups were evaluated using Pearson chi-square and linear-by-linear associations for univariate analyses. Results were considered significant when P was <0.05. Multivariate analyses were performed using logistic regression. The agreement between TST and QFT-GIT was investigated using kappa statistics (16).

Between 8 October 2004 and 3 February 2006, 909 subjects were included. Of these, 171 were recruits and 674 were employees that had recently returned from missions; 34 were tested routinely for other reasons; and for 30 participants, these data are missing. Demographic characteristics are reported in Table 1.

TST results were available for 676/746 (90.6%) subjects (Fig. 1). The TST was not performed in 163 subjects, 128 of whom were BCG vaccinated while 35 were known to have previous TST conversions. Using ≥10 mm and ≥15 mm as the TST cutoffs, 139/676 (20.6%) and 51/676 (7.5%) subjects, respectively, were positive by TST (Table 2).

Analyzed by TST category, the distributions of TST results among subjects returning from missions and recruits were significantly different with an equally distributed higher percentage in each TST category with a value of >0 among subjects returning from missions (Table 1) (P < 0.001).

In univariate analysis, the duration of the mission and birth in a high-endemicity region for TB were predictive of a positive TST result (data not shown). After adjusting for the day of inclusion in the study in a multivariate analysis, reported contact with the local population was the only parameter that was significantly associated with a positive TST result.

Positive QFT-GIT results were obtained in 33/909 (3.6%) participants. Among recruits, 5/171 results were positive (2.9%); of these recruits, two had previously been treated for TB. Of the remaining three recruits, one was foreign born. Among subjects returning from missions, 28/738 (3.8%) had
positive QFT-GIT results, which was not different from the percentage among recruits. Nine of those 28 (32.1%) reported past treatment for LTBI 1 to 14 years previously compared to 1.6% (14/682) of the participants negative by QFT-GIT. A total of 10.7% (3/28) reported contact with individuals smear positive for TB before their missions compared to 6.7% (55/821) of the group negative by QFT-GIT. Since 12 of 28 (42.9%) positive QFT-GIT results were thus explained by the medical histories, the actual risk of recent infection during a mission was at most 16/725 (2.2%) (or lower if LTBI had been acquired between enrollment in the armed forces and the mission). After an adjustment for day of blood sampling in the multivariate analysis, no parameters were found to be associated with the QFT-GIT result (data not shown).

Results for both TST and QFT-GIT were available for 676 subjects, 20.6% of whom had a positive TST at a cutoff of 10 mm and 3.1% of whom had a positive QFT-GIT result (Table 2). The overall agreement between TST and QFT-GIT was 82% ($\kappa = 0.19$); when using 15 mm as the cutoff, the agreement was 92% ($\kappa = 0.24$) (Table 2).

Among subjects with a TST result of at least 10 mm, 44.4% (4/9) of the recruits were positive by QFT-GIT compared to 11.5% (15/130) of participants returning from missions ($P = 0.001$). When using 15 mm as the cutoff, the agreement was 92% ($\kappa = 0.24$) (Table 2).

Discordance analysis (Table 3) showed that discordant results were more frequent among subjects returning from missions compared to those among recruits.

In this study, the low overall agreement of 82% ($\kappa = 0.19$)
between the TST and QFT-GIT test was explained by a high number of discordant TST-positive, QFT-GIT-negative results. At the ≥10-mm cutoff, subjects returning from missions had a fourfold higher rate of positive TST results, whereas the rate of positive QFT-GIT results was about fourfold lower compared with those of new recruits. Notably, among participants positive by TST, 44.4% of recruits had positive QFT-GIT results compared with 11.5% for subjects returning from missions, confirming that most TST conversions after missions were false-positive results caused by exposure to nontuberculous mycobacteria (3). Assuming that most positive TST results among recruits truly indicated LTBI, the 11.5% positive QFT-GIT results among subjects returning from missions reflected the expression 100/44.4 × 11.5% (thus, 25% with true LTBI). This implies that 75% of the observed positive TST results among these BCG-unvaccinated subjects were probably false positive.

A limited number of studies have used QFT-GIT in comparison with TST (2, 4–6, 8, 11, 13). It appeared that the agreement between the TST and QFT-GIT results was strongly dependent on the clinical-epidemiological setting, with the prevalence of TB and BCG vaccination status among the studied population as important determinants (5, 8, 11). Agreement was higher in studies of persons at significant risk for infection, and lower values were found among BCG-vaccinated subjects.

The U.S. Centers for Disease Control and Prevention recommend that QFT-G be used instead of the TST in all circumstances in which the TST is currently used (10). United Kingdom guidelines issued by The National Institute for Health and Clinical Excellence instead recommend a two-stage strategy of TST, followed by an interferon gamma release assay to confirm a positive TST result (12). In the military setting of large-scale screenings and low a priori risk of LTBI, logistic problems could argue against the use of blood tests for general screening. With a two-stage approach, however, it must be taken into account that the rate of TST reading can be low.

In conclusion, a positive TST result was significantly less frequently associated with a positive QFT-GIT result among subjects returning from missions than among recruits. This suggests that false-positive TST results are frequent after missions. In this setting, QFT-GIT could guide more targeted treatment of individuals with actual LTBI and risk of TB.

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**TABLE 3. Distribution of concordant and discordant results for TST and the QFT-GIT test**

| Parameter                        | No. of subjects | % of subjects with TST/QFT-GIT results that were*: | Concordant vs discordant P value |
|----------------------------------|-----------------|--------------------------------------------------|---------------------------------|
|                                  |                 | Neg/Neg   Pos/Pos   Pos/Neg   Neg/Pos               |                                 |
| Gender                           | Male            | 607        79.4     2.6       17.6     0.3               | 0.535                           |
|                                  | Female          | 66         77.3     4.5       18.2     0.0               |                                 |
| TB incidence in birth country cases | 10              | 660        79.7     2.6       17.4     0.3               | 0.297                           |
|                                  | 10–49           | 2          100.0    0.0       0.0     0.0               |                                 |
|                                  | 50–99           | 4          50.0     0.0       50.0     0.0               |                                 |
|                                  | 100–199         | 5          40.0     20.0      40.0     0.0               |                                 |
|                                  | ≥200            | 5          60.0     20.0      20.0     0.0               |                                 |
| Have visited tropics             | No              | 531        80.0     2.4       17.1     0.4               | 0.363                           |
|                                  | Yes             | 141        76.6     4.3       19.1     0.0               |                                 |
| Contact with TB-infected individuals | No              | 648        79.8     2.5       17.4     0.3               | 0.226                           |
|                                  | Yes             | 28         64.3     10.7      25.0     0.0               |                                 |
| Treated for TB or LTBI           | No              | 669        79.2     2.5       17.9     0.3               | 0.247                           |
|                                  | Yes             | 7          71.4     28.6      0.0     0.0               |                                 |
| History of positive TST result   | No              | 645        81.9     1.9       16.1     0.3               | 0.000                           |
|                                  | Yes             | 27         25.9     22.2      51.9     0.0               |                                 |
| Went on mission                  | No              | 18         38.9     11.1      50.0     0.0               | 0.000                           |
|                                  | Yes             | 498        77.1     2.6       19.9     0.4               |                                 |
| Recruits                         |                 | 145        93.8     2.8       3.4      0.0               |                                 |
| Location of mission              | Bosnia          | 36         44.4     5.6       50.0     0.0               | 0.000                           |
|                                  | Kyrgyzstan      | 21         76.2     0.0       23.8     0.0               |                                 |
|                                  | Iraq            | 165        83.6     2.4       12.7     1.2               |                                 |
|                                  | Afghanistan     | 269        77.7     2.6       19.7     0.0               |                                 |
| Duration mission (mo)            | 0–4             | 308        81.2     2.3       16.2     0.0               | 0.032                           |
|                                  | 4–6             | 176        72.2     2.3       25.0     0.6               |                                 |
|                                  | >6              | 16         56.3     12.5      31.3     0.0               |                                 |

*a* Neg, negative; Pos, positive.
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