Clinical trial paper

# Comparison of latent tuberculosis infection rate between contacts with active tuberculosis and non-contacts

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## ABSTRACT

Background: Latent tuberculosis infection (LTBI) rate is usually high in contacts with infectious TB patients. In TB-prevalent country, however, background LTBI rate is already high in general population.
Aim: To compare the LTBI rate between controls and recognized close contacts.
Method: Between February 2010 and January 2014, 183 controls and 376 contacts with TB infection were enrolled. The tuberculin skin test (TST) and QuantiFERON®-TB Gold In-Tube (QFT-GIT) were used to diagnose LTBI.
Results: Higher TST positivity was found in the control group than in the contact group (37.7% vs. 29.9%, $P = 0.073$). The positive QFT-GIT rate was higher in contacts than in controls (32.6% vs. 24.1%, $P = 0.054$). A significantly higher positive QFT-GIT rate was found in contacts under 30 years of age than in controls (16.1% vs. 0%, $P = 0.005$).
Conclusion: In a TB-prevalent country, both TST and QFT-GIT were limited in the diagnosis of recent LTBI in adult contacts probably due to the high background LTBI rate. However, QFT-GIT seems to be better than TST in differentiating LTBI status in contacts younger than 30 year old.

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## 1. Introduction

Tuberculosis (TB) remains an important cause of infectious disease and is a major public health problem worldwide. In 2012, an estimated 8.6 million new TB cases and 1.3 million TB deaths were reported [1]. Approximately, one-third of the world's population is infected with Mycobacterium tuberculosis. Several factors have been associated with the progression of latent TB infection (LTBI) to active TB disease [2]. The first step in the development of active TB is a contact with an infectious TB patients, followed by acquisition of TB infection [3]. Therefore, the early detection and treatment of LTBI in individuals who have close contact with pulmonary TB patients is crucial to reduce the risk of developing active TB disease. Although there is no standard for identifying LTBI, traditionally the most frequently used LTBI screening method is the tuberculin skin

test (TST) [3]. The interferon-gamma release assay (IGRA) is a new tool available for the identification of LTBI in clinical practice [4]. Recent guidelines released by World Health Organization recommend evaluation and management of LTBI should be performed in adults and child contacts of pulmonary TB cases in at least upper middle-income countries with estimated TB incidence less than 100 per 100,000 population [5].

In South Korea, an intermediate TB-burden country, the annual incidence of TB is approximately 92 per 100,000 general population. Screening for LTBI using TST or IGRA has been performed in patients at high risk for developing TB including household close contacts, military personnel, school children, anti-tumor necrosis factor users, or transplant recipients in South Korea [6—12]. More recently, revised guidelines for the diagnosis and treatment of LTBI recommend screening based on TST or IGRA in subjects at a high risk of TB infection or active TB disease [13]. The last nationwide prevalence survey on TB infection based on TST was reported in 1995 [14], and since then the LTBI prevalence of the general population is not well-known.

One very important group to test is close contacts to infectious TB cases. However, in South Korea there is concern that positive TST

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rates may not be significantly different between contacts and non-contacts probably due to high BCG vaccination status whereas IGRA test may reveal the difference in the positive rate between contacts and non-contact. However, this hypothesis has not been investigated yet.

The aim of this study was to investigate the prevalence of LTBI between subjects without and those with recognized contact with culture confirmed pulmonary TB patients using both the TST and the QuantiFERON®-TB Gold In-Tube (QFT-GIT).

## 2. Materials and methods

### 2.1. Subjects

Subjects who had close contact with culture-positive pulmonary TB patients (designated as contact group) were enrolled at Asan Medical Center from February 2010 to January 2013. Subjects who had no recognized recent contact with infectious TB patients, who were not at high risk for developing TB, and who hoped to screen for TB infection voluntarily were enrolled as a control group during the same period at Hapcheon-Gun Public Health Center and Asan Medical Center. The reason why control subjects were screened for LTBI at Hapcheon-Gun Public Health Center was to survey the prevalence of LTBI in this area. Only subjects who visited either center for reasons other than respiratory symptoms or TB screening were selected as controls. Exclusion criteria were a history of previous pulmonary TB or refusal of LTBI screening. Clinical data were retrospectively collected from the subjects: age, gender, smoking status, comorbidities, history of Bacillus Calmette-Guerin (BCG) vaccination, and presence of a BCG scar. Medical records were reviewed retrospectively.

The study was approved by the Institutional Review Board of the Asan Medical Center. Written informed consent was waived due to the retrospective nature of the analysis. This study was conducted in accordance to the amended Declaration of Helsinki.

### 2.2. Definition of close contact

All household contacts with an exposure to culture-positive active pulmonary TB patients were considered as close contacts. A close contact was defined as having a cumulative exposure time over 8 h if the index case is smear positive or over 40 h if the index case is smear negative, irrespective of household or non-household contact [15].

### 2.3. Measurement of LTBI

#### 2.3.1. TST

Each TST was performed by intradermal injection of 2 tuberculin units of purified protein derivative (PPD) RT23 (Statens Serum Institute, Copenhagen, Denmark) into the forearm using the Mantoux technique [16,17]. Results of TST were recorded in millimeter (mm) of induration. Reactions were evaluated 48−72 h after injection, with a positive result defined as an induration of $\geq 10$ mm in the transverse diameter. Because of the high BCG vaccination rate, Korean guidelines recommend 10 mm as a cut-off of TST induration. TST was measured by a well-trained nurse but it was not confirmed by another nurse [13].

## 3. QFT-GIT

QFT-GIT (Cellestis, Carnegie, Victoria, Australia) assay was performed in 2 stages, according to the manufacture's instructions. Blood was drawn at the time of TST application. One-milliliter aliquots of blood were drawn directly into three evacuated blood collection tubes, one containing heparin alone (negative control), one containing T cell mitogen (positive control), and one containing M. tuberculosis specific antigens, including early secreted antigenic target 6, culture filtrate protein 10, and TB7.7 (TB-antigen tube). Following overnight incubation, 200 μl of plasma was removed from each well and the concentration of interferon-gamma (IFN-γ) was determined by enzyme-linked immunosorbent assay, with a positive response defined as an antigen-nil IFN-γ concentration $\geq 0.35$ IU/ml [18].

### 3.1. Statistical analysis

Comparison between groups was made using the $\chi^2$ tests for categorical variables and Mann−Whitney $U$ test for non-categorical variables. kappa (κ) coefficients were used to measure concordance between TST and QFT-GIT results and were classified as follows: κ > 0.75 defined as excellent agreement, κ between 0.4 and 0.75 defined as fair to good agreement, and κ < 0.4 defined as poor agreement [19]. Logistic regression analysis was used to evaluate predictors for positive test results. All tests of significance were two-sided; $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version18.0 (SPSS Inc., Chicago, IL, USA).

## 4. Results

### 4.1. Characteristics of the index cases

Mean age was 51.5 ± 18.1 years and 63.5% (122/192) were male. In 26.3% (49/186) of subjects, the radiologic extent was moderately advanced, and cavity lesions were present in 26.3% (49/186) of patients. Positive acid-fast bacillus (AFB) smears of sputum were revealed in 43.2% (83/192) of patients. Among the index cases, multidrug-resistant TB comprised 30.2% of total index cases.

### 4.2. Comparison of clinical and sociodemographic characteristics in controls and close contacts

Of the 559 patients enrolled in the study, 183 were controls and 376 were contacts. Table 1 shows the clinical features, TST and QFT-

**Table 1**
Comparison of clinical characteristics, tuberculin skin test and QuantiFERON®-TB Gold In-Tube results between controls and contacts with pulmonary tuberculosis.

| Variables | Controls | Contacts* | P-value |
|---|---|---|---|
| | n = 183 | n = 376 | |
| Male gender | 74 (40.4) | 133 (35.4) | 0.245 |
| Mean age, years | 40.2 ± 19.5 | 37.4 ± 20.8 | 0.127 |
| Age range, (years) | | | 0.272 |
| 0−14 | 23 (12.6) | 72 (19.1) | |
| 15−29 | 34 (18.6) | 62 (16.5) | |
| 30−39 | 30 (16.4) | 70 (18.6) | |
| 40−49 | 29 (15.8) | 45 (12.0) | |
| 50−59 | 29 (15.8) | 66 (17.6) | |
| ≥60 | 38 (20.8) | 61 (16.2) | |
| Ever-smoker | 21 (11.5) | 69 (18.4) | 0.038 |
| Comorbidities | 22 (12.0) | 27 (7.2) | 0.058 |
| BCG vaccination | 126 (69.2) | 344 (92.0) | <0.001 |
| Positive TST | 63/167 (37.7) | 110/368 (29.9) | 0.073 |
| TST induration size, mean (mm) | 7.0 ± 9.2 | 5.9 ± 7.3 | 0.661 |
| Positive QFT-GIT | 41/170 (24.1) | 97/298 (32.6) | 0.054 |
| QFT-GIT level, IU/ml | 0.63 ± 1.56 | 1.09 ± 2.36 | 0.049 |

Data are expressed as a number (n, %) unless otherwise indicated. Comorbidities include diabetes mellitus, malignancy, or immunocompromized status. QFT-GIT = QuantiFERON®-TB Gold In-Tube; TST = tuberculin skin test; BCG = Bacilli de Calmette-Guerin. *The majority (369/376) of contacts were household contacts.