The Prevalence and Risk Factors of Latent Tuberculosis Infection among Health Care Workers Working in a Tertiary Hospital in South Korea

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Introduction

Compared to general population, health care workers (HCWs) are at increased risk of tuberculosis (TB) infection through occupational exposure to TB patients. Considering that about 5%–15% of TB infected people are at risk for developing TB during their lifetime, HCWs with latent TB infection (LTBI) are potential risk group for TB leading to transmission of Mycobacterium tuberculosis to other HCWs and patients. Therefore, LTBI screening and treatment for HCWs is an important component of TB infection control measures in the hospitals.

In hospitals, many HCWs from different occupations are
working in various departments. And, studies conducted in South Korea have reported varying prevalence of LTBI among HCWs from 17% to 37%. Therefore, it is important to find out who is at high risk for TB infection in order to determine the priority of LTBI screening and treatment.

Because the risk of TB infection depends on the proximity and duration of exposure to infectious TB patients, HCWs working in the respiratory medicine, emergency department, medical intensive care unit, pulmonary function test and bronchoscopy unit and laboratory processing suspected or confirmed M. tuberculosis specimens are known to be at high risk of TB infection. Thus, the Korea Centers for Disease Control and Prevention (KCDC) recommended that HCWs working in the departments with increased risk of TB infection (TB-related departments) receive annual screening for LTBI.

Recently, interferon-gamma release assay like QuantiFERON-TB Gold In-Tube (QFT-GIT) is widely used for the diagnosis of LTBI because it has several advantages over the tuberculin skin test (TST) such as higher specificity without cross-reactivity with bacillus Calmette–Guérin strains or environmental mycobacteria. And, several studies targeting HCWs have suggested that a positive QFT-GIT result is a better indicator of LTBI than a positive TST result.

To date, the risk factors of TB infection of HCWs using QFT-GIT have not been thoroughly evaluated in South Korea, an intermediate TB burden country with the annual notification rate of new TB cases as 60.4 per 100,000 population in 2016. Therefore, analyzing the prevalence and various risk factors of TB infection of HCWs, including current working in the TB-related departments, is important for determining the priority for LTBI screening and treatment in South Korea.

This study assessed the prevalence and the risk factors for LTBI, including current working in the TB-related departments, among HCWs working in a tertiary referral hospital in South Korea.

### Materials and Methods

#### 1. Study subjects and design

This cross-sectional study was conducted from June 2017 to December 2017 in a 700-bed tertiary referral hospital in South Korea. Approximately 350 TB patients are treated at the hospital annually. Of the 540 HCWs involved in the patient care, 515 underwent QFT-GIT test according to the national LTBI screening program, excluding 25 HCWs who had history of TB treatment or were positive for previous LTBI test (TST or interferon-γ release assay). They also underwent chest radiography to exclude active TB. Of the 515 HCWs who underwent QFT-GIT test, 499 agreed to participate in the study. A questionnaire was administered to each participant to collect demographic data and known risk factors of TB infection; occupation (doctor, nurse, paramedical personnel), specific departments in which they work, duration of employment as a HCW, experience of exposure to pre-treatment TB patients both inside and outside the hospital. The departments of the hospital were divided into TB-related and TB-unrelated departments according to KCDC recommendation. TB-related departments include outpatient and inpatient departments of respiratory medicine and infection, outpatient department of pediatric respiratory medicine, pulmonary function test and bronchoscopy unit, emergency department, medical intensive care unit, chest section of radiology department, microbiology section of laboratory. TB-unrelated departments include outpatient and inpatient departments of internal medicine and pediatrics not included in the TB-related departments, obstetrics, and gynecology, etc. The study protocol was approved by the Institutional Review Board of the Dankook University Hospital (2017-06-013) and written informed consents were provided by all participants.

#### 2. QuantiFERON-TB Gold In-Tube test

QFT-GIT was used for the diagnosis of LTBI in this study. QFT-GIT test was performed according to the manufacturer’s recommendations (Qiagen Ltd., Carnegie, VIC, Australia). The blood samples were mixed with M. tuberculosis specific antigens (early secreted antigenic target-6, culture filtrate protein 10, and TB 7.7), mitogen phytohemagglutinin (positive control) and saline (negative control) and incubated for 16-24 hours. The detection and quantification of interferon-gamma by enzyme-linked immunosorbent assay was used to measure in vitro responses to TB antigens. All values were interpreted after subtracting the value of the negative control. The QFT-GIT test results were interpreted as positive if the interferon-γ level in response to TB antigen ≥0.35 IU/mL and >25% of Nil value.

#### 3. Statistical analysis

Data are expressed as a number (%) or median (range or interquartile range). All statistical analyses were performed using the SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Comparison between HCWs working in the TB-related and TB-unrelated departments were analyzed using the chi-square test for categorical variables. Continuous variables were analyzed using Mann-Whitney U test. Risk factors for LTBI were evaluated using logistic regression analysis. Independent variables for multivariate analysis were selected on the basis of their statistical significance in univariate analysis and clinical significance. A two-tailed p-value of <0.05 was considered to be statistically significant.
Results

1. Characteristics of participants

Of the 499 participants, 428 (85.8%) were female and the median age was 31.0 years (range, 20–67 years). The median length of employment as a HCW was 7.0 years (range, 1–38 years). The occupations of the HCWs included 54 doctors (10.8%), 365 nurses (73.1%), and 80 paramedical personnel (16.0%) (radiology and laboratory technicians, nursing assistants, etc.). All were human immunodeficiency virus test negative. Nine (1.8%) were medicated with diabetes mellitus, and 18 (3.6%) were current smoker. Of the 499 participants, the prevalence of LTBI based on QFT-GIT positivity was 15.8%. There were no radiologically active TB patients among the participants.

2. Prevalence of LTBI and comparisons between HCWs working in the TB-unrelated and related departments

Clinical characteristics of 291 HCWs working in the TB-unrelated departments and 208 HCWs working in the TB-related departments are shown in Table 1. The median age of HCWs working in the TB-unrelated and related departments was 32.0 years (range, 20–64 years) and 30.0 years (range, 20–67 years), respectively. The median length of work as a HCW in the TB-unrelated and related departments was 7.0 years (range, 1–38 years) and 6.0 years (range, 1–35 years), respectively. There were no differences between the two groups in age (Figure 1), duration of work as HCWs (Figure 2), and sex. But, prevalence of experience of exposure to pre-treatment TB patients was higher in HCWs working in the TB-related departments than in the HCWs working in the TB-unrelated departments (78.8% vs. 61.9%, p<0.001). More doctors were included in the TB-unrelated departments and more paramedical personnel were included in the TB-related departments. The prevalence of LTBI among HCWs working in the TB-related departments was higher than that of HCWs working in the TB-unrelated departments, but it was not statistically significant (17.3% vs. 14.8%, p=0.458).

3. Risk factors for LTBI

On univariate logistic regression analysis, age (odds ratio [OR], 1.094; 95% confidence interval [CI], 1.064–1.124) and duration of work as HCW (OR, 1.096; 95% CI, 1.065–1.128) were significantly associated with increased risk of LTBI (Table 2). Other known risk factors such as current working in the TB-related departments, occupation, experience of exposure to pre-treatment TB patients were not associated with increased risk of LTBI. Multivariate analysis showed that only age was independently associated with increased risk of LTBI (OR, 1.069; 95% CI, 1.019–1.121) (Table 3).

Discussion

LTBI treatment is known to be one of the important strategies to prevent the development of TB and block the transmission of M. tuberculosis to other people. However, since the benefit of LTBI treatment is not prominent compared to the cost for screening and treatment for LTBI, LTBI screening and treatment is generally recommended for people whose benefit outweighs the cost. It is therefore important to determine who is at high risk for TB infection in order to select the target groups for LTBI screening and treatment.

In general, HCWs working in the TB-related departments are known to be at high risk for TB infection. Thus, the KCDC recommended that HCWs who are working in the TB-related departments receive annual screening for LTBI. As expected, this study showed that experience of exposure to pre-treatment TB patients were more frequent in HCWs working in the TB-related departments than HCWs working in the TB-unrelated departments (78.8% vs. 61.9%). Considering that TB patients have the highest infectivity before treatment, this finding suggests that HCWs working in the TB-related departments are at higher risk of TB infection than those working in the TB-unrelated departments.

This study showed that the prevalence of LTBI among HCWs working in the TB-related departments was higher than that of HCWs working in the TB-unrelated departments, but unexpectedly it was not statistically significant (17.3% vs. 14.8%, p=0.458). Possible explanations for this unexpected result are as follows. In large hospitals, HCWs may work in several departments in rotation. And, HCW might have moved from TB-unrelated department to TB-related department recently. Considering that it takes about 8 weeks for QFT-GIT conversion after exposure to infectious TB patients, QFT-GIT may give false-negative result if it is conducted during the window period. Considering the high prevalence of TB in South Korea, it seems that out-hospital exposure to TB patients also diluted the difference between the two groups. In a multicenter study conducted in South Korea also showed that current working in the TB-related departments was not associated with positive QFT-GIT result. However, HCWs with experience of working in the TB-related departments was independently associated with positive QFT-GIT result. Another study conducted at a tertiary hospital in South Korea showed that the positive rate QFT-GIT was higher among HCWs who had frequent direct contact with TB patients in the TB-related departments than those who had no history of direct contact with TB patient in the TB-unrelated departments. Another study conducted in military hospitals of South Korea also showed that the risk of LTBI was higher in HCWs who took care of TB patients for one year or more. These findings suggest that longer duration of work in the TB-related departments is better risk factor of LTBI than the current working in the TB-related departments in South Korea.
The transmission of TB in the hospital is also affected by the efficiency of TB infection control measures. In resource-limited countries, HCWs are at increased risk of exposure to TB patients within the hospitals due to lack of isolation rooms and inadequate TB infection control measures. In these settings, LTBIs among HCWs was consistently associated with markers of occupational exposure to TB patients such as working in TB clinic, long duration of employment as HCW. However, in resource-rich countries, the risk of TB infection among HCWs becomes closer to general population because

| Table 1. Clinical characteristics and QuantiFERON-TB Gold In-Tube results of participants |
|-----------------------------------------|----------------------------------|----------------------------------|----------------------------------|-----|
| Characteristic                          | All participants (n=499)          | TB-unrelated departments (n=291) | TB-related departments (n=208)   | p-value* |
| Age, median (range), yr                 | 31.0 (20 to 67)                  | 32.0 (20 to 64)                  | 30.0 (20 to 67)                  | 0.498 |
| <30                                     | 233 (46.7)                       | 135 (46.4)                       | 98 (47.1)                        | 0.959 |
| 30-39                                   | 114 (22.8)                       | 65 (22.3)                        | 49 (23.6)                        |       |
| 40-49                                   | 126 (25.3)                       | 76 (26.1)                        | 50 (24.0)                        |       |
| ≥50                                     | 26 (5.2)                         | 15 (5.2)                         | 11 (5.3)                         |       |
| Sex                                     |                                  |                                  |                                  |       |
| Male                                    | 71 (14.2)                        | 38 (13.1)                        | 33 (15.9)                        | 0.436 |
| Female                                  | 428 (85.8)                       | 253 (86.9)                       | 175 (84.1)                       |       |
| Occupation                              |                                  |                                  |                                  |       |
| Doctor                                  | 54 (10.8)                        | 39 (13.4)                        | 15 (7.2)                         | 0.001 |
| Nurse                                   | 365 (73.1)                       | 219 (75.3)                       | 146 (70.2)                       |       |
| Paramedical personnel                   | 80 (16.0)                        | 33 (11.3)                        | 47 (22.6)                        |       |
| Years working as HCW, median (range)    | 7.0 (1 to 38)                    | 7.0 (1 to 38)                    | 6.0 (1 to 35)                    | 0.405 |
| Years working as HCW                    |                                  |                                  |                                  |       |
| <5                                      | 206 (41.3)                       | 117 (40.2)                       | 89 (42.8)                        | 0.921 |
| 5-9                                     | 91 (18.2)                        | 56 (18.9)                        | 36 (17.3)                        |       |
| 10-19                                   | 100 (20.0)                       | 60 (20.6)                        | 40 (19.2)                        |       |
| ≥20                                     | 102 (20.4)                       | 59 (20.3)                        | 43 (20.7)                        |       |
| Experience of exposure to pre-treatment TB patients | | | |       |
| No                                      | 155 (31.1)                       | 111 (38.1)                       | 44 (21.2)                        | <0.001 |
| Yes                                     | 344 (68.9)                       | 180 (61.9)                       | 164 (78.8)                       |       |
| Current smoking                         |                                  |                                  |                                  |       |
| No                                      | 481 (96.4)                       | 280 (96.2)                       | 201 (96.6)                       | >0.999 |
| Yes                                     | 18 (3.6)                         | 11 (3.8)                         | 7 (3.4)                          |       |
| Co-morbidities                          |                                  |                                  |                                  |       |
| No                                      | 490 (98.2)                       | 286 (98.3)                       | 204 (98.1)                       | >0.999 |
| Yes                                     | 9 (1.8)                          | 5 (1.7)                          | 4 (1.9)                          |       |
| QFT-GIT level, median (IQR), IU/mL      | 0.010 (−0.003 to 0.088)          | 0.010 (−0.002 to 0.063)          | 0.010 (−0.003 to 0.117)          | 0.400 |
| QFT-GIT result                          |                                  |                                  |                                  |       |
| Negative                                | 420 (84.2)                       | 248 (85.2)                       | 172 (82.7)                       | 0.458 |
| Positive                                | 79 (15.8)                        | 43 (14.8)                        | 36 (17.3)                        |       |

Values are presented as number (%) unless otherwise indicated.

*p-values compare between TB-unrelated and TB-related departments.

TB: tuberculosis; HCW: health care worker; QFT-GIT level: QuantiFERON-TB Gold In-Tube level (TB Ag-Nil); IQR: interquartile range.
transmission of TB in the hospitals is reduced or prevented by implementation of effective TB infection control measures. In a study conducted in the United States, a resource-rich country, showed that non-occupational factors such as old age and foreign birth account for most of TB infections arising among HCWs. In most tertiary hospitals in South Korea, including the hospital included in this study, patients diagnosed or suspected of having TB are admitted to isolation rooms equipped with negative pressure ventilation until they are no longer infectious. And HCWs and visitors entering such rooms are required to wear N95 respirators. In the present study, known risk factors for TB infection such as current working in the TB-related departments, experience of exposure to pre-treatment TB patients were not associated with increased risk of LTBI among HCWs. These findings suggest that TB infection control measures employed by the hospital of this study have mitigated the transmission of TB in the hospital.

| Characteristic                        | OR (95% CI)   | p-value |
|--------------------------------------|---------------|---------|
| Age                                  | 1.094 (1.064–1.124) | <0.001 |
| Male sex                             | 1.372 (0.722–2.605) | 0.334 |
| Occupation                           |               |         |
| Doctor                               | -             | -       |
| Nurse                                | 0.715 (0.338–1.509) | 0.378 |
| Paramedical personnel                | 1.277 (0.538–3.031) | 0.579 |
| Experience of exposure to pre-treatment TB patients | 1.116 (0.658–1.896) | 0.683 |
| Current working in the TB-related department | 1.207 (0.744–1.958) | 0.445 |
| Duration of work as HCW              | 1.096 (1.065–1.128) | <0.001 |
| Current smoking                      | 2.115 (0.732–6.110) | 0.166 |
| Co-morbidity (DM)                    | 1.532 (0.312–7.516) | 0.599 |

Table 2. Univariate logistic regression analysis of risk factors for latent TB infection among HCWs

| Characteristic                        | OR (95% CI)   | p-value |
|--------------------------------------|---------------|---------|
| Age                                  | 1.069 (1.019–1.121) | 0.006 |
| Duration of work as HCW              | 1.033 (0.982–1.087) | 0.209 |
| Experience of exposure to pre-treatment TB patients | 0.776 (0.435–1.385) | 0.392 |
| Current working in the TB-related department | 1.309 (0.775–2.212) | 0.314 |

Table 3. Multivariate logistic regression analysis of risk factors for latent TB infection among HCWs

TB: tuberculosis; HCW: health care worker; OR: odds ratio; CI: confidence interval; DM: diabetes mellitus.
Latent tuberculosis infection among HCWs\textsuperscript{5,22}.

It is generally known that there is a correlation between LTBI prevalence among HCWs and regional TB prevalence because high prevalence of TB in the community increases the risk of TB infection of HCWs both inside and outside of the hospital\textsuperscript{22}. Therefore, national TB control programs to reduce the incidence of TB in the community also reduce the risk of TB infection for HCWs. The South Korean government has implemented various TB control programs, including LTBI screening and treatment for HCWs, to reduce the incidence of TB, and it has been steadily declining in recent years\textsuperscript{22}. The results of this study can be used as a useful data for the government of South Korea to establish LTBI screening and treatment programs for HCWs.

The purpose of conducting LTBI screening and treatment for HCWs is to block the spread of TB by preventing infected persons from progressing to active TB. However, currently available diagnostic tests for LTBI have several limitations; variable specificity, cannot distinguish between LTBI and active TB, do not predict who will progress to active TB, controversies on the conversion from negative to positive result\textsuperscript{23}. Thus LTBI screening and treatment should be targeted to HCWs at high risk for LTBI and progression to active TB. However, it is not well known who is at increased risk of developing active TB among LTBI positive HCWs. Therefore, further study is needed on the risk factors for predicting who will develop active TB among LTBI positive HCWs.

The limitation of this study is that participants of this study did not undergo LTBI screening before starting work at the hospital. Therefore, it is not possible to exclude the possibility that a QFT-GIT positive HCW has already been infected with \textit{M. tuberculosis} before starting work at the hospital. And since this study was conducted only in a single tertiary hospital, it is difficult to say that the people who participated in this study represent the HCWs of South Korea in general. Therefore, in order to better understand the pattern and risk factors of LTBI of HCWs in South Korea, multi-center prospective studies are needed for HCWs who are LTBI test negative when they start working at the hospital\textsuperscript{15,23}.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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