T-SPOT®-TB Test for Latent Tuberculosis Infection Diagnosis and Treatment Guidance in Thai Health-Care Professionals

To The Editor,

We read with interest the articles by Kumar et al. and Anwar et al. published recently in this journal.[1,2] The articles indicate the high rates of latent tuberculosis infection (LTBI) among health-care professionals (HCPs) of 19% using tuberculin skin test (TST) in India[1] and 9.1% and 34.6% using TST and QuantiFERON-TB Gold In-Tube Test (QFT-GIT), respectively, in Egypt.[2] The infections were found to be associated with gender, place of residence, education, profession, work duration, work commute time, marital status, smoking, and infection control practices.[1,2] These study results underscore the importance of screening and treatment for LTBI as TB preventive strategies among HCPs. Either TST or interferon-γ-release assays (IGRAs) can be used for LTBI testing and guiding treatment among HCPs depending on availability and appropriateness in each setting. However, a reliable serial LTBI testing for conversion (changing from a negative result to a positive result) is needed.

A study from a TB endemic setting demonstrated the annual conversion rate of 13–22% using IGRAs and 38% using TST as a LTBI serial test among HCPs,[3] while the conversion rates in TB low prevalence settings were 6.1–8.3% and 0.5–2.5% using IGRAs and TST, respectively.[4,5] The poor agreement between IGRAs and TST as a serial LTBI test indicates some limitations of both tests. False nonreactivity of baseline TST (due to little or no response when TST is performed only once) can lead to falsely high conversion rates in TB-endemic settings when the follow-up TST becomes reactive.[3,4] For an IGRA, QFT-GIT, the fluctuation of interferon-γ level, especially around the cutoff level can result in high rates of conversion and reversion (changing from a positive result to a negative result) in both TB-endemic and low prevalence settings.[3,4] Nonetheless, performance of another IGRA, T-SPOT.TB Test (T-SPOT) as a serial test has been less studied with limited data on false conversion and reversion.[3,5]

We conducted a prospective cohort study among HCPs of a Thai tertiary-care center from May 01, 2016 to May 31, 2017. The study was approved by the Faculty of Medicine, Thammasat University Ethics Committee. All HCPs aged ≥18 years were screened and those who had history of TB, were treated for TB or LTBI or had any LTBI testing within 12 months was excluded. After obtaining the informed consent from the eligible HCPs, a survey form asking about TB-related exposures and infection control practices was distributed to and completed by each HCP. All HCPs underwent active TB screening based on their symptoms and a chest radiograph. T-SPOT®-TB Test (Oxford Immunotec Ltd., UK) was used for LTBI screening. Test procedures and interpretation were according to the standard guideline.[7] The HCPs who had positive T-SPOT were offered 9-month isoniazid preventive therapy (IPT). All participating HCPs were assessed for occurrence of TB, TB risk exposures, and infection control practices via the similar survey form and medical record review during 1-year follow-up. Repeat T-SPOT was performed at 1 year after the initial test. Statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA).

A total of 166 HCPs were screened for eligibility and 140 HCPs were included [Figure 1]. Of the 140 HCPs included, 83 (59%) were physicians, 50 (36%) were nurses, and the median age was 27 years (IQR 25–31 years). Most of the HCPs reported history of TB contact (95%), especially contacts with smear-positive pulmonary TB patients (59%) and inconsistent use of N95 mask when contacted with TB patients (91%). At baseline, the positive rate of T-SPOT was 23/140 (16%). Eighty-nine HCPs (64%) underwent T-SPOT at baseline and follow-up 1 year later while 51 HCPs (36%) did not present for the follow-up test. Comparing between the HCPs with and without follow-up T-SPOT, those who underwent follow-up test had significantly longer median working duration (48 vs. 26 months; P = 0.02) and higher frequency of TB contact (P = 0.04).

Among the 89 HCPs with baseline and follow-up T-SPOT tests, 63 (71%) had persistent negative T-SPOT, 12 (13%) had persistent positive T-SPOT, 9 (10%) had T-SPOT conversion, and 5 (6%) had T-SPOT reversion. At baseline, the HCPs with persistent positive T-SPOTs were significantly older, had longer median working duration, and were more likely to report respiratory contact with secretions of patients with pulmonary TB. All of the nine HCPs with T-SPOT conversion reported significant contacts with patients who had active pulmonary TB (100%) and most reported inconsistent use of appropriate personal protection equipment (67%). During 1-year follow-up period, there were no significant differences in characteristics, frequency, and duration of TB contact and use of N95 mask between the four groups. However, the incidence of tuberculosis was higher among HCPs with T-SPOT conversion compared to HCPs with persistent positive T-SPOT, HCPs with T-SPOT reversion, and HCPs with persistent negative T-SPOT (22 vs. 8 vs. 0 vs. 0 cases/100 person-years, respectively; P = 0.004).

The 17 HCPs with baseline positive T-SPOT (12 with persistent positive T-SPOT and five with T-SPOT reversion) were offered IPT. Of these 17 HCPs, eight (47%) completed 9-month IPT, eight (47%) declined IPT, and one (6%) did not complete

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IPT (IPT discontinued at 3 months due to asymptomatic elevation of liver enzymes) [Figure 1]. The IPT completion rate was lower in HCPs with persistent positive T-SPOT than that of HCPs with T-SPOT reversion (25% vs. 100%). Comparing between the HCPs who completed IPT and those who declined or did not complete IPT, the HCPs who completed IPT had significantly lower incidence of TB (0 vs. 11 cases/100 person-years; \( P < 0.001 \)) and higher rate of T-SPOT reversion \( [5/8 (63\%) \text{ vs. } 0/9 (0\%); \ P = 0.009] \).

In the TB-endemic setting where most HCPs reported significant work-related TB exposures, the highest risk of TB development was observed in HCPs with T-SPOT conversion followed by those with persistent positive T-SPOT while the risk was lowest in HCPs with T-SPOT reversion and with persistent negative T-SPOT. This finding may suggest the utility of T-SPOT in identifying and monitoring HCPs who were at-risk for TB development. In this study, we used the interval of 1 year for retesting and found the low rate of follow-up for retesting among the HCPs. These results underscore the need for education to promote LTBI treatment and appropriate infection control practices for TB prevention among the HCPs while the appropriate intervals of T-SPOT retesting and assessment for TB risk are yet to be determined.

We observed the lower TB incidence among HCPs with persistent positive T-SPOT and T-SPOT reversion compared to those with T-SPOT conversion. Given that most of these HCPs were given IPT after their baseline positive results, the lower TB incidence was most likely due to the TB prevention effect of IPT. During the 1-year follow-up period, we found the possible association between T-SPOT reversion and no occurrence of active TB. This may suggest the use of T-SPOT in monitoring IPT effectiveness and is consistent with findings from other studies which QFT-GIT were evaluated.\(^8,9\) When comparing characteristics, TB exposures, and infection control practices during the follow-up period, we found that older age, longer working duration, and respiratory contact with secretion from patients with pulmonary TB were associated with persistent positive T-SPOT result. These may suggest the ongoing TB exposures associated with these HCP characteristics.\(^10\) Such TB exposures may obscure the change of T-SPOT results despite IPT, resulting in persistent positivity of T-SPOT.

This study has some recognizable limitations including recall biases from self-report information, the small sample size of each HCP group with different T-SPOT results, and limited generalizability to other settings. Nonetheless, the study’s findings may suggest the utility of T-SPOT in diagnosing LTBI,
guiding IPT and identifying HCPs with subsequent risk for TB in an Asia-Pacific TB-endemic setting. Additional studies with larger sample size and in other settings are needed to confirm the effectiveness of T-SPOT-guided preventive therapy and serial testing among HCPs in this region.

Acknowledgments
Some parts of this study were presented as poster presentation at the IDWeek 2018, October 3–7, 2018, San Francisco, CA, USA.

Declaration of patient consent
The authors certify that they have obtained all appropriate participant consent forms. In the form, the participant(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The participant understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
This study was partly supported by the National Institute of Health, Ministry of Public Health of Thailand.

Conflicts of interest
There are no conflicts of interest.

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Submitted: 10-Dec-2019 Revised: 12-Dec-2019 Accepted: 07-Jan-2020 Published: 18-Mar-2020

REFERENCES
1. Kumar MG, Joseph B, Goud BR, Joseph M, Rajitha M. Risk of tuberculosis infection among healthcare workers in a tertiary-care hospital in Bengaluru City. Indian J Occup Environ Med 2019;23:83-9.
2. Anwar MM, Ahmed DM, Elareed HR, Abdel-Latif RA, Sheemy MS, Kamel NM, et al. Screening of latent tuberculosis among healthcare workers in a Egyptian hospital using tuberculin skin test and QuantiFERON-TB Gold In-Tube test. Indian J Occup Environ Med 2019;23:106-11.
3. Adams S, Ehrlich R, Baatjies R, van Zyl-Smit RN, Said-Hartley Q, Dawson R, et al. Incidence of occupational latent tuberculosis infection in South African healthcare workers. Eur Respir J 2015;45:1364-73.
4. Lucet JC, Abitboul D, Estellat C, Roy C, Chollet-Martin S, Tubach F, et al. Interferon-γ release assay vs. tuberculin skin test for tuberculosis screening in exposed healthcare workers: A longitudinal multicenter comparative study. Infect Control Hosp Epidemiol 2015;36:569-74.
5. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, et al. Interferon-γ release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. Am J Respir Crit Care Med 2014;189:77-87.
6. Whitaker JA, Mirtschulava V, Kipiani M, Harris DA, Tabagari N, Kempker RR, et al. Prevalence and incidence of latent tuberculosis infection in Georgian healthcare workers. PLoS One 2013;8:e58202.
7. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection–United States. MMWR Recomm Rep 2010;59:1-25.
8. Khawcharoenporn T, Phetsuksiri B, Rudeeaneksin J, Srisungngam S, Apisarnthanarak A. QuantiFERON-TB Gold In-Tube test for tuberculosis prevention in HIV-infected patients. Jpn J Infect Dis 2017;70:502-6.
9. Lee SH, Lew WJ, Kim HJ, Lee HK, Lee YM, Cho CH, et al. Serial interferon-gamma release assays after rifampicin prophylaxis in a tuberculosis outbreak. Respir Med 2010;104:448-53.
10. Ringshausen FC, Nienhaus A, Schablon A, Schlösser S, Schultzze-Werninghaus G, Rohde G. Predictors of persistently positive Mycobacterium tuberculosis-specific interferon-gamma responses in the serial testing of health care workers. BMC Infect Dis 2010;10:220.

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How to cite this article: Khawcharoenporn T, Aksornchindarat W, Yodpinij N, Srisungngam S, Rudeeaneksin J, Bunchoo S, et al. T-SPOT® TB test for latent tuberculosis infection diagnosis and treatment guidance in Thai health-care professionals. Indian J Occup Environ Med 2020;24:47-9.