

Proposal to Revise the Screening Test for Latent Tuberculosis Infection in Close Contacts at Elementary Schools in Korea

Jong-Myon Bae

Department of Preventive Medicine, Jeju National University School of Medicine, Jeju, Korea

The 2018 National Guideline for Tuberculosis Control, which was published by the Korea Centers for Diseases Prevention and Control (KCDC), mandates conducting an epidemiological survey among close contacts of active tuberculosis patients at public institutions such as schools. In the procedure for these surveys, the tuberculin skin test (TST) is mandated as the screening test for latent tuberculosis infection in elementary school students. However, several guidelines recommend using the interferon-gamma releasing assay (IGRA) for contacts aged over 5 years with a Bacillus Calmette–Guérin vaccination history. The main reason for this is that IGRA has a higher specificity and lower false positive rate than TST. In addition, IGRA requires only a single visit to draw blood and the results are available within 24 hours. These advantages could promote cooperation from both parents and students in conducting these surveys. Thus, these findings regarding the benefits of IGRA for surveys of close contacts at elementary schools should be incorporated into the KCDC guideline.

Key words: Latent tuberculosis, Mycobacterium tuberculosis, Practice guideline, Tuberculin test, Interferon-gamma release tests

CURRENT GUIDELINES ON EPIDEMIOLOGICAL SURVEYS FOR CONTROLLING TUBERCULOSIS AT PUBLIC INSTITUTIONS IN SOUTH KOREA

Because South Korea (hereafter Korea) has consistently been ranked high in major tuberculosis (TB) indices among Organization for Economic Cooperation and Development countries, the Korea Centers for Disease Control and Prevention (KCDC)

Received: February 24, 2019 Accepted: May 8, 2019

Corresponding author: Jong-Myon Bae, MD, PhD
Department of Preventive Medicine, Jeju National University School of Medicine, 102 Jejudaehak-ro, Jeju 63243, Korea

E-mail: jmbae@jejunu.ac.kr

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

established 'Phase 1 of the National Guideline for Tuberculosis Control' in 2013 to strengthen processes regarding epidemiological surveys on TB at public institutions such as schools and military bases [1]. The purpose of these surveys is to stop the spread of TB by screening for active tuberculosis patients (ATBPs) among close contacts of the index patient and to prevent disease progression by identifying cases with latent tuberculosis infections (LTBIs) [1]. In other words, these surveys aim to enable the early diagnosis and response to ATBPs and LTBIs, to allow preventive measures to be taken, as well as to promote treatment of index patients.

According to page 146 of the guideline for the epidemiological surveys [1], anyone who contacts an index patient is initially subject to a chest X-ray test (CXR) to assess whether active TB is present. For the diagnosis of LTBI, the tuberculin skin test (TST) is utilized for elementary-school students, and the interferon-gamma releasing assay (IGRA) or a combined

TST/IGRA test is used for middle-school students and beyond.

The current guideline tailors its approach according to subjects' chronological age by following the principle of 'requiring' a TST for children younger than 5 years of age and 'recommending' a TST for children between 5 years and 18 years of age [1]. However, the above principle leaves open the possibility that IGRA could be used for elementary-school students between the ages of 6 and 12 instead of TST. In other words, the idea of utilizing IGRA as the primary LTBI screening method should be revisited as an alternative, or supplement, to the current practice of using a TST in contacts between the ages of 6 and 12 because IGRA was developed to overcome the limitations of TST [2]. Furthermore, other guidelines [3,4] state that IGRA is preferable to TST in contacts above the age of 5 who have a positive history of *Bacillus Calmette–Guérin* (BCG) vaccination.

Ethics Statement

This paper is a perspective so it did not need ethical consideration.

EVIDENCES FOR SELECTING A LATENT TUBERCULOSIS INFECTION SCREENING METHOD IN ELEMENTARY STUDENTS

The potential benefits of utilizing IGRA instead of TST in identifying LTBI in elementary-school students are supported by the following 4 considerations.

First, because the purpose of these epidemiological surveys is to screen close contacts to identify infected individuals, it is reasonable for an epidemiological survey to utilize a test with higher specificity. This is based on the fact that roughly 10-30% of contacts of ATBPs, who are actively shedding pathogens, become infected [5]. In other words, the goals of epidemiological surveys at public institutions can be more efficiently achieved if the utilized method can initially exclude the 70-90% of contacts who are not infected (about 2.3-9.0 times more prevalent than the infected) from the 10-30% who are infected. Furthermore, early notification of clearance to the subjects and their parents can improve their cooperation with the survey, and can also minimize any disturbances to their education by providing them with early emotional comfort [6]. Because TST and IGRA have similar sensitivity (75-85% and 80-85%, respectively) in Korean elementary-school students who

receive mandatory BCG vaccinations, while the specificity of IGRA (89-100%) is significantly higher than that of TST (49-65%) [4,7], it is reasonable to consider utilizing IGRA as an alternative to TST.

Second, only approximately 10% of carriers who test positive for LTBI progress to full-blown active TB [5]. However, the positive predictive value (PPV) for identifying the 10% of cases that do progress is very low for both TST (1.5%) and IGRA (2.7%) [8]. Therefore, implementing IGRA, which has the higher PPV, as the primary screening method in elementary-school students can help students and parents to better understand the results of the screening examination.

Third, in an effort to compensate for the aforementioned low PPV, IGRA can be conducted among high-risk groups [7] or be supplemented with TST in the combined TST/IGRA method [1]. However, page 108 of the KCDC guideline requires TST to be used as the primary screening method in elementary-school students and calls for immediate LTBI treatment without further examinations if a child tests positive in the initial TST. Therefore, an effort must be made to enhance the PPV by conducting supplemental IGRA testing in patients with positive TST results, even if TST is used as the primary method. Moreover, implementing an additional screening method with lower false positive results can reduce unnecessary drug administration. Minimizing false positive results requires a test with a higher specificity. Because IGRA has a higher specificity than TST, it is a more suitable candidate as a primary screening method [4,7]. Additionally, IGRA is not susceptible to confounding variables, such as the universal positive history of BCG vaccination in Korean elementary students and exposure to atypical mycobacteria, which are known to increase the frequency of false positive results in TST. Therefore, IGRA should be selected in preference to TST [4].

Fourth, the KCDC guidelines [1] require all epidemiological surveys to send out letters of notification to TB contacts along with the necessary questionnaires, to host information sessions for parents, and to obtain informed consent for LTBI treatment. The success of epidemiological surveys targeting elementary students depends heavily on positive understanding and active cooperation from both students and their parents [6]. Thus, IGRA can induce a better reception of the survey than TST for the following reasons [7]: (1) TST requires at least 2 visits for the examination and results, while IGRA only requires a single visit; (2) TST results are available in 48-72 hours, whereas IGRA takes less than 24 hours; and (3) while IGRA has

a standardized protocol for interpretation, TST has standards that vary depending on the circumstances and is subject to error depending on the reader.

PROPOSAL TO IMPLEMENT INTERFERON-GAMMA RELEASING ASSAY AS THE LATENT TUBERCULOSIS INFECTIONS SCREENING METHOD IN ELEMENTARY-SCHOOL STUDENTS

Given the 4 arguments presented above, IGRA is preferable to TST as a screening test for LTBI in elementary students in Korea. Taking into consideration the universal mandatory BCG vaccination program in Korea and the current practice of using the combined TST/IGRA method, further research is needed to establish grounds for the combined IGRA/TST method, in which IGRA (with the higher PPV) is applied first and is supplemented by TST if necessary.

The main limitations in implementing IGRA include the issues of age limitations, blood collection, and cost [2]. As for the issue of age limitations, IGRA is not recommended in children under 5 years of age because their weak cellular immune response often yields indeterminate results [9]. However, because the main focus of this discussion is elementary school contacts who are 6 years of age or older, this age limitation should not impede the implementation of IGRA as the primary LTBI screening method. Regarding the issue of blood collection, an experienced phlebotomist, with appropriate parental consent, would find it easier to collect samples from elementary students than from children under the age of 5. Finally, although IGRA is more expensive per person than TST, it is known to have a higher cost-effectiveness in high-risk groups that have had close contact with ATBPs. Furthermore, the combined TST/IGRA method has been shown to be more cost-effective than standalone TST because it reduces the unnecessary administration of prophylactic anti-TB medications [10]. Further research that takes into account the specific circumstances of Korea is needed to identify subjects' receptiveness and the cost-effectiveness of implementing IGRA as the method used before TST.

In conclusion, both evidence-based and value-based appraisals suggest that the benefits of using IGRA as the LTBI screening modality prior to TST outweigh its cost in Korean elementary-school students who receive BCG vaccinations as part of the national mandatory vaccination program.

SUPPLEMENTAL MATERIALS

Korean version is available at <https://doi.org/10.3961/jpmph.19.043>.

CONFLICT OF INTEREST

The author has no conflicts of interest associated with the material presented in this paper.

ACKNOWLEDGEMENTS

This research was supported by the 2019 scientific promotion program funded by Jeju National University.

AUTHOR CONTRIBUTIONS

All work was done by JMB.

ORCID

Jong-Myon Bae <https://orcid.org/0000-0003-3080-7852>

REFERENCES

1. Korea Centers for Disease Control and Prevention. National guideline for tuberculosis control, 2018 [cited 2019 Jul 20]. Available from: http://www.cdc.go.kr/board.es?mid=a20507020000&bid=0019&act=view&list_no=138005 (Korean).
2. Chawla H, Lobato MN, Sosa LE, ZuWallack R. Predictors for a positive QuantiFERON-TB-Gold test in BCG-vaccinated adults with a positive tuberculin skin test. *J Infect Public Health* 2012; 5(6):369-373.
3. Kitai I, Morris SK, Kordy F, Lam R. Diagnosis and management of pediatric tuberculosis in Canada. *CMAJ* 2017;189(1):E11-E16.
4. Hartman-Adams H, Clark K, Juckett G. Update on latent tuberculosis infection. *Am Fam Physician* 2014;89(11):889-896.
5. Korea Centers for Disease Control and Prevention. A to Z of latent tuberculosis infection [cited 2019 Jul 20]. Available from: http://www.cdc.go.kr/board.es?mid=a20501000000&bid=0015&act=view&list_no=143180 (Korean).
6. Gu H. News: students were tested after teachers. *JIBS*; 2018 Dec 28 [cited 2019 Feb 20]. Available from: <http://www.jibs.co.kr/news/replay/viewNewsReplayDetail/2018122821491458590?feed=na> (Korean).

7. Starke JR; Committee On Infectious Diseases. Interferon- γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics* 2014;134(6):e1763-e1773.
8. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon- γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. *Chest* 2012;142(1):63-75.
9. Moon HW, Hur M. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection: an updated review. *Ann Clin Lab Sci* 2013;43(2):221-229.
10. Soysal A, Türel O, Toprak D, Bakir M. Comparison of positive tuberculin skin test with an interferon-gamma-based assay in unexposed children. *Jpn J Infect Dis* 2008;61(3):192-195.