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1 **Latent tuberculosis infection screening and treatment in congregate settings (TB FREE**  
2 **COREA): protocol for a prospective observational study in Korea**

3

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18

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20

1 **Abstract**

2 **Introduction:** South Korea regards tuberculosis (TB) incidence in congregate settings as a serious  
3 problem. To this end, systematic latent TB infection (LTBI) diagnosis and treatment were provided  
4 to approximately 1.2 million individuals in high risk congregate settings.

5 **Methods and analysis:** We designed a prospective cohort study of individuals tested for LTBI,  
6 based on the data collected on all persons screened for LTBI as part of the 2017 congregate settings  
7 program in South Korea. Four types of databases are kept: LTBI screening database (personal  
8 information and LTBI test results), national health information (NHI) database (socio-  
9 demographic data and comorbidities), public healthcare information system (PHIS) database, and  
10 the Korean national TB surveillance system (KNTSS) database (TB outcomes). Information  
11 regarding LTBI treatment at private hospitals and public health centres is collected from NHI and  
12 PHIS databases, respectively. The screening data are cleaned, duplicates are removed, and, where  
13 appropriate, re-coded to analyse specific exposures and outcomes. The primary objective is to  
14 compare the number of active TB cases prevented within two years between participants  
15 undergoing treatment and not undergoing treatment in the LTBI screening program in congregate  
16 settings. Cascade of care for LTBI diagnosis and treatment will be evaluated among those with a  
17 positive LTBI test result. A Cox proportional hazards model will be applied to determine the risk  
18 factors for developing active TB.

19 **Ethics and dissemination:** The protocol is approved by the institutional review boards of Incheon  
20 St. Mary's Hospital, the Catholic University of Korea. Study results will be disseminated through  
21 peer-reviewed journals and conference presentations.

22 **Trial Registration number:** KCT0003905

23

24 **Keywords:** tuberculosis, cohort, incidence, prevalence, risk factor, big data

25

1 **Strengths and limitations of this study**

- 2 ● This is a prospective cohort study involving a very large number of people from the  
3 general population in an intermediate tuberculosis (TB) burden.
- 4 ● Long-term follow-up of a large number of participants is possible, and all TB cases can  
5 be investigated during the follow-up period because of the unique linkage of electronic  
6 databases.
- 7 ● Data regarding anti-latent TB treatment are indirectly collected based on insurance claims;  
8 therefore, treatment adherence cannot be assessed.
- 9 ● Details of specific clinical data, such as adverse drug reactions and laboratory findings,  
10 are not attainable.
- 11 ● This is an observational study without associated mathematical modelling, thus the impact  
12 of the latent TB infection screening programme can only be examined on the individual  
13 level, not at the population level through the prevention of transmission.

14

15

## 1 INTRODUCTION

2 Approximately one quarter of the world's population is estimated to have latent tuberculosis  
3 infection (LTBI),<sup>1</sup> which is defined as a state of persistent immune response to stimulation by  
4 *Mycobacterium tuberculosis* antigens without clinical evidence of active tuberculosis (TB).<sup>2</sup>  
5 Although the treatment of active TB remains a top priority in endemic settings, this approach alone  
6 is not sufficient to achieve steep annual reductions in incidence necessary to reach the World  
7 Health Organization (WHO) End TB Strategy targets; thus, prevention of active TB by treatment  
8 of LTBI is critical.<sup>3</sup> Mathematical modelling has shown that protecting 8% of people with LTBI  
9 each year from developing active TB disease could result in a 14-fold decrease in the global  
10 incidence of TB in 2050 compared to the incidence in 2013.<sup>4</sup> WHO recommends that testing and  
11 treatment of LTBI should be offered to both adult and child contacts of pulmonary TB cases in  
12 high-income or upper middle-income countries with an estimated TB incidence rate of less than  
13 100 per 100,000 population, such as South Korea.<sup>5</sup>

14 South Korea has the highest TB incidence and mortality rates among high-income countries.  
15 Driven by strong political will,<sup>6</sup> South Korea has strengthened its TB policy, resulting in a 5.2%  
16 reduction annually in the incidence of newly reported TB cases from 2011 to 2016. Recently, TB  
17 outbreaks among health workers in medical institutions and postpartum care centres have become  
18 an important social issue, which has raised public awareness and influenced further government  
19 commitment. Based on the experience of the Korea Centers for Disease Control and Prevention  
20 (KCDC) from 2013 in proactive contact investigations in congregate settings and influenced by  
21 the WHO guidelines,<sup>5</sup> the 'TB Free Korea program' was started in 2017. As a part of this program,  
22 systematic LTBI testing and preventive TB treatment were provided to approximately 1.2 million  
23 individuals in designated high-risk congregate settings.

24 The introduction of the management of LTBI as a public health intervention requires program  
25 monitoring in order to evaluate quality, effectiveness, and impact.<sup>7</sup> Operational research efforts to  
26 enable the effective delivery of such interventions based on setting-specific context and disease  
27 epidemiology need to be an integral part of the programmatic management of LTBI<sup>8</sup>. Further  
28 scientific evidence to help understand LTBI is essential to optimize its management and update  
29 the guidelines. Here, we hypothesized that systematic LTBI testing and preventive treatment in  
30 congregate settings would reduce the national level of active TB incidence. We designed a

1 prospective cohort to evaluate short- and long-term effects of this project. In this manuscript, we  
2 provide an overview of the design, methods, and scope of this cohort study.

3

## 4 **METHODS AND ANALYSIS**

### 5 **Aims and objectives**

6 From 2017, we started recruiting a cohort of people who underwent Interferon-Gamma Release  
7 Assay (IGRA) testing during the LTBI screening program in the congregate settings. Our primary  
8 objective is to compare the number of active TB cases prevented within two years between  
9 participants who receive LTBI treatment and those who do not. Other key objectives to be  
10 addressed in this cohort study are as follows: (1) to determine the prevalence of LTBI among  
11 participants at the initial screening; (2) to determine the prevalence of concurrent active TB among  
12 participants at the initial screening; (3) to follow up with the cohort and identify the incidence of  
13 new LTBI cases; and (4) to follow up with the cohort and identify the incidence of new active TB.  
14 We also aim to assess the risk factors for both LTBI prevalence and incidence and evaluate  
15 outcomes along the cascade of care of LTBI as secondary outcomes. As long-term follow-up is  
16 possible with the use of the large interlinked healthcare databases implemented in South Korea, it  
17 is possible to examine different outcomes at specific time points (Table 1).

18

### 19 **Study setting and population**

20 Our prospective cohort study is based on data systematically collected on all patients within the  
21 South Korean LTBI screening program in congregate settings in 2017. According to the WHO's  
22 Global Tuberculosis Report, the incidence of TB was 100 per 100,000 population in 2011, which  
23 decreased to 77 persons per 100,000 population in 2016. However, because of recent stagnation in  
24 these declines, the government revised the TB Prevention Act in 2016 to require LTBI screening  
25 for employees in high-risk congregate settings. High risk settings are defined as follows: (1)  
26 workers in medical institutions, postpartum care centres, kindergartens, childcare centres, schools,  
27 and welfare facilities; (2) people in correctional facilities; and (3) military conscripts and first-year

1 high school students. The existing employees in these congregate settings were screened in the  
2 government program as of 2017.<sup>9</sup>

3

#### 4 **Database linkage**

5 In this study, we will use four databases: the LTBI screening database from the government  
6 program, the national health information (NHI) database,<sup>10</sup> the public healthcare information  
7 system (PHIS) database,<sup>11</sup> and the Korean national TB surveillance system (KNTSS) database  
8 (Figure 1 and Table 2). Anonymised joint keys, which replace the personal identification numbers  
9 assigned to the residents of Korea, are used to link the LTBI screening database with three other  
10 databases through deterministic matching. This process has been given ethical approval.<sup>10</sup>

11 KCDC collects data from the participants in the LTBI screening program and manages the LTBI  
12 screening database, which contains personal information (gender, age, types of congregate settings,  
13 etc.) and the results of IGRA and chest x-rays. Information regarding LTBI treatment (regimen  
14 and completion) at private hospitals and public health centres are collected from the NHI and PHIS  
15 databases, respectively. Socio-demographic data, such as residential area, insurance types, and  
16 income level, and comorbidities based on International Classification of Disease-10 (ICD-10)  
17 codes are also available in the NHI database established by Korean National Health Insurance  
18 Service. At the public health centres, additional information regarding LTBI treatment, such as  
19 adverse drug reactions and causes of treatment withdrawal, is collected and stored in the PHIS  
20 database. The KNTSS database is a web-based notification system, which receives data regarding  
21 all patients who are diagnosed with or treated for TB in South Korea.<sup>12</sup> The notification data  
22 include personal information, microbiological examination results, anti-TB treatment regimens,  
23 and final treatment outcomes.

24

#### 25 **Systematic TB screening algorithm**

26 Participants in the LTBI screening program were assessed for TB infection according to the  
27 Korean National TB guidelines.<sup>13</sup> After excluding active TB cases based on clinical assessment  
28 (previous TB treatment history, contact history, respiratory symptoms related to TB, physical



1 examination) and chest x-ray, LTBI testing was conducted using IGRA. The QuantiFERONTB-  
2 Gold In-Tube tests (QGIT, Qiagen, Hilden, Germany) and the interpretation of results were  
3 performed according to the manufacturer's instructions.

4

## 5 **LTBI treatment regimens**

6 LTBI treatment is offered based on the Korean National TB guidelines,<sup>13 14</sup> which recommend  
7 isoniazid monotherapy for 9 months, rifampin monotherapy for 4 months, or isoniazid and  
8 rifampin combination therapy for 3 months based on the clinician's decision. Because of the  
9 difficulty in communicating effectively with, and delivering information on LTBI concepts to,  
10 healthcare professionals, a nationwide education program was implemented in 2017.<sup>6</sup> A network  
11 with over 300 hospitals was organized for the treatment of LTBI cases identified through the  
12 screening program. Participants could be referred to private hospitals and public health centres for  
13 LTBI treatment without restriction.

14 We will use the NHI and PHIS databases to extract data regarding LTBI treatment at private  
15 hospitals and public health centres. We will define individuals as under treatment of LTBI if they  
16 have ICD-10 code R76.80 and are prescribed isoniazid, rifampin, or a combination of isoniazid  
17 and rifampin. Those who started LTBI treatment were categorized into three groups: completion  
18 group, withdrawal group, and on-treatment group. Individuals are considered to have completed  
19 therapy if they are prescribed more than 80% of total doses within 12 months for isoniazid therapy,  
20 6 months for rifampicin therapy, or 4 months for isoniazid and rifampin combination therapy.<sup>13</sup>

21

## 22 **Definition of active TB cases**

23 Notification data from the KNTSS database are primarily used in order identify active TB cases.  
24 As active TB cases are notified to and monitored by the KNTSS under Korean law, the  
25 completeness and timeliness values for TB notification in the KNTSS are high,<sup>12</sup> assuring its  
26 reliability. The NHI database is also used to identify non-notified active TB cases, types of anti-  
27 TB drugs, and treatment adherence based on insurance claims. The diagnosis of active TB is  
28 identified using ICD-10 codes (A15-19) and subsequently confirmed by prescriptions for  $\geq 3$  anti-

1 TB drugs. The anti-TB drugs include isoniazid, rifampin, ethambutol, pyrazinamide, amikacin,  
2 kanamycin, streptomycin, quinolones, thionamide, cycloserine, and para-aminosalicylic acid. The  
3 accuracy of identifying active TB cases based on the NHI database was validated and has been  
4 used in previous studies on TB.<sup>15 16</sup> In order to classify previous and active cases, we will identify  
5 the notification date of active TB case per individual and examine a temporal relationship between  
6 the notification date and the LTBI test date. We will define a new active TB case as one notified  
7 more than 30 days after the LTBI test date and a concurrent active TB case as one notified within  
8 30 days of the LTBI test date. If the notification occurred before the LTBI test date, we will  
9 consider an individual to have had previous anti-TB treatment. Those with a previous history of  
10 anti-TB treatment, who were identified using the KNTSS and NHI databases, will be excluded.  
11 Those with active TB notified within 30 days of the LTBI test will also be excluded as we assume  
12 that they had subclinical TB infection at the time of screening.

13

#### 14 **Independent variables**

15 Factors that might influence the incidence of active TB, such as gender, age, income level,  
16 comorbidities, or history of close contact with active TB, will be collected and used as independent  
17 variables. Income level was described by means of ventiles, with each income ventile consisting  
18 of 5 % of the population. Income level was then categorized into four groups: low (ventiles 1–5),  
19 lower-middle (6–10), upper-middle (11–15), and high (16–20). Comorbidities were selected based  
20 on guidelines published by the WHO, National Institute for Health and Care Excellence (NICE),  
21 and Center for Disease Control and Prevention.<sup>17</sup> Comorbidities were identified based on ICD-10  
22 codes and claims of procedures and prescribed drugs via Korean electronic data interchange (KEDI)  
23 codes, such as HIV infection, organ transplant, silicosis, end-stage renal disease, head and neck  
24 cancer, diabetes mellitus, hematologic malignancy, those having anti-TNF blockers, long-term  
25 steroids, or chemotherapy, and those with a previous history of gastrectomy.

26

#### 27 **Analysis of baseline data**

28 The screening data will be cleaned, duplicates removed, and, where appropriate, recoded to analyse  
29 specific exposures and outcomes.

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*(1) To determine the prevalence of LTBI among participants at the initial screening*

The primary outcome of prevalent LTBI will be defined as positive results of IGRA among participants at the initial screening.

$$\text{prevalence of LTBI} = \frac{\text{no. of participants with a positive IGRA test except those with history of TB treatment}}{\text{overall no. of participants except those with a history of TB treatment}}$$

As a secondary outcome, multivariable logistic regression analysis adjusted for independent variables will be used to assess the risk factors for the prevalence of LTBI.

*(2) To determine the prevalence of concurrent active TB among participants at the initial screening*

The prevalence of active TB is calculated as the number of concurrent active TB cases divided by the number of all participants, except those with a history of TB treatment.

$$\text{prevalence of active TB} = \frac{\text{no. of participants with concurrent active TB cases except those with history of TB treatment}}{\text{overall no. of participants except those with a history of TB treatment}}$$

**Analysis of follow-up data**

*(1) Cascade of care in LTBI*

Those with a positive LTBI test result will be followed-up, and the cascade of care for LTBI diagnosis and treatment will be evaluated.<sup>18</sup> Specific outcomes of interest include the following: (1) the number of people eligible for testing for LTBI; (2) the number who initiated and completed screening with IGRA; (3) the number with positive results with IGRA who had chest x-ray and medical evaluation; and (4) the number who were prescribed, started, and completed treatment for LTBI. We will also identify the completion rates of LTBI treatment by regimens.

*(2) To follow-up the cohort and identify incidence of new LTBI cases*

1 Individuals enter the cohort at the date of their LTBI test. In congregate settings such as medical  
2 institutions, participants with a negative initial IGRA test result will receive serial IGRA tests  
3 annually. The incidence of LTBI will be defined as positive conversion at a later IGRA test and  
4 expressed as the number of newly diagnosed LTBI cases per 100,000 person-years. The  
5 denominator, total person-time at risk, is the sum of total time contributed by those with negative  
6 results of initial IGRA test, except those with a history of TB treatment and concurrent active TB  
7 cases. If a new LTBI case does not occur, the last date of the serial IGRA test is the final follow-  
8 up date.

9 
$$\text{incidence of LTBI} = \frac{\text{no. with a positive conversion at a later IGRA test}}{\text{total person-time at risk (PY)}}$$

10 When serial follow-up of IGRA test is not performed annually, we will use the mid-point between  
11 the latest-negative and earliest-positive test dates as the date of the infection event in order to  
12 estimate the incidence<sup>19</sup>. However, if the testing rate drops below 80%, sensitivity analysis will be  
13 conducted.

14

15 *(3) To follow-up the cohort and identify incidence of new active TB*

16 Individuals enter the cohort at the date of their LTBI test and exit upon notification of death or  
17 becoming an active TB case. If an active TB case does not occur, the last updated date of the  
18 KNTSS database is the final follow-up date. We will follow the individuals in order to identify a  
19 new case of active TB after 12, 24, and 60 months of LTBI testing (Figure 2). The incidence of  
20 active TB is expressed as the number of new active TB cases per 100,000 person-years. The  
21 denominator, total person-time at risk, is the sum of total time contributed by all participants,  
22 except those with a history of TB treatment and concurrent active TB cases.

23 
$$\text{incidence of active TB} = \frac{\text{no. of new active TB cases}}{\text{total person - time at risk (PY)}}$$

24 Individuals with new active TB will be categorized into four groups based on the IGRA test results  
25 and LTBI treatment: (1) those with negative IGRA test results; (2) those with positive IGRA test  
26 results who do not start LTBI treatment; (3) those with positive IGRA results who start and  
27 complete LTBI treatment; and (4) those with positive IGRA results who start but do not complete  
28 LTBI treatment. After testing for proportional hazards, a Cox proportional hazards model will be

1 applied to determine the risk factors for developing active TB, if appropriate. Cumulative TB  
2 incidence curves will be generated using the Kaplan-Meier method, and differences between  
3 groups will be analysed using the log-rank test. The primary outcome is to compare the active TB  
4 incidence between treated IGRA-positive participants and untreated IGRA-positive participants.  
5 We will calculate the incidence rate of disease progression in IGRA-positive versus IGRA negative  
6 individuals, separately in the former instance by individuals who did and did not undergo treatment.  
7 Among individuals who underwent treatment, figures will also be stratified by treatment regimen.  
8 We will calculate positive and negative predictive values of the IGRA test for predicting active  
9 TB incidence in the absence of treatment.

10

### 11 **Patient and public involvement**

12 Patients were not involved in setting the research question, the outcome measures, the design, or  
13 implementation of the study. We plan to translate the results into short, easy-to-read summaries  
14 and disseminate it to the relevant patient community through local media.

15

### 16 **ETHICS AND DISSEMINATION**

17 The protocol has been approved for its scientific content and compliance with human subject  
18 research regulations by the institutional review boards of Incheon St. Mary's Hospital, the Catholic  
19 University of Korea. These committees waived the need for written informed consent from the  
20 study participants because this research involves the collection of publicly available and  
21 anonymous data. The investigators will disseminate the findings of this research through  
22 publication in a peer-reviewed journal and via conference presentations, including to key national  
23 stakeholders. In compliance with the policy of the International Committee of Medical Journal  
24 Editors, this study was registered with the Clinical Research Information Service, Republic of  
25 Korea (cris.nih.go.kr, KCT0003905) in May of 2019.

26

### 27 **DISCUSSION**

1 The KCDC created a TB epidemic investigation team in 2013, which performs proactive contact  
2 investigations in congregate settings at the national level. There have been improvements in the  
3 early detection of active TB cases and prevention of its transmission at schools. However,  
4 continued TB outbreaks at various congregate settings, such as neonatal intensive care units and  
5 postpartum care centres, have become a social issue.<sup>20 21</sup> As the problem became more prominent,  
6 the Korean government has regarded TB incidence in congregate settings as a serious problem and  
7 made efforts to it more actively. Thus, mandatory screening for TB infection for workers in  
8 facilities (medical institutions, postnatal care centres, kindergartens, childcare centres, schools,  
9 welfare facilities, and correctional facilities), military conscripts, and first-year high school  
10 students has been adopted since 2017 as a part of the ‘TB free Korea program’.<sup>6</sup> Postpartum care  
11 centres, kindergarten, childcare centres, and schools were selected because of their high risk for  
12 TB transmission, especially among infants and children with low immunity. In order to prevent  
13 nosocomial TB transmission, healthcare workers at hospitals were also target populations for the  
14 screening of TB infection. Military conscripts were selected because of the unique environment of  
15 the military units, such as confined living settings and proximity.<sup>22</sup> First-year high school students  
16 were also included because they are at the age when TB cases begin to increase rapidly. To  
17 successfully implement the LTBI screening program in congregate settings and carry out the South  
18 Korea LTBI policy, programmatic management should include monitoring and evaluation systems.  
19 Based on the results of the present study, we expect to provide scientific evidence enabling us to  
20 better understand the LTBI burden in South Korea and assess the clinical and epidemiological  
21 impact of the LTBI screening program.

22 Because of high incidence of nosocomial TB infection among healthcare workers<sup>23</sup> and delay in  
23 isolating active pulmonary TB patients admitted to hospitals<sup>24</sup> in South Korea, the Korean TB  
24 guideline highlights the importance of serial IGRA testing for high-risk healthcare workers and  
25 recommend treating those with positive conversion. However, recent studies suggest that serial  
26 IGRA testing results in an over-diagnosis of LTBI<sup>25</sup> and are not cost-effective<sup>26</sup> in the North  
27 American setting. We plan to conduct sensitivity analysis using the different cut-offs for  
28 conversion or confirmatory tests, which were suggested to mitigate the over-diagnosis of LTBI.

29 Korea underwent short-term but intense socioeconomic changes after liberation from the Japanese  
30 occupation during World War II. In parallel with economic prosperity, South Korea achieved

1 admirable control of TB in the past half century.<sup>27</sup> Based on this rapid change in the socioeconomic  
2 status in South Korea, age-period-cohort modelling can clarify the relative and independent effects  
3 of influential exposures shared by each birth cohort and influential exposures experienced by all  
4 birth cohorts on TB incidence over time.<sup>28 29</sup> As long-term follow-up of our cohort is feasible, we  
5 can identify biological, historical, and socioeconomic determinants in long-term trends of TB  
6 status and provide evidence for designing effective TB policies and public health interventions  
7 based on age-period-cohort analysis.

8 There are several key strengths of the current ‘TB FREE COREA’ study. First, it is a cohort study  
9 involving a very large number of people from the general population. Previous work has been  
10 undertaken in mainly immune-compromised high-risk groups or small hospital-based cohorts.<sup>30</sup>  
11 The outcomes of our study can offer rich insights into the intermediate- or low-risk groups of LTBI  
12 within an intermediate TB-burden country, such as South Korea. Second, it is a prospective study  
13 designed by a multidisciplinary team of clinicians, epidemiologists, statisticians, and other related  
14 experts. When designing the study protocol, we set specific goals and selected several key  
15 questions in order to plan data collection suitable for each key question. Third, an active TB case  
16 is a nationally notifiable disease and is monitored by the KNTSS. All the cases diagnosed and  
17 treated under the national health insurance system are recorded in the NHI database. Thus, using  
18 data-linkage between the unique electronic databases KNTSS and NHI, all TB cases can be  
19 scrutinized during the follow-up period, thereby minimising the loss of detecting new cases. Fourth,  
20 long-term follow-up of a large number of participants is possible because of the unique electronic  
21 database of the NHI. This database has been extensively used to establish basic platforms for  
22 customized retrospective cohort data.<sup>10</sup> A periodic monitoring and evaluation process will be  
23 undertaken by the advisory boards.

24 Despite these strengths, the major limitation of the present study is that we receive only a limited  
25 dataset of clinical, social, and demographic information. The details regarding adverse drug  
26 reactions during the preventive therapy are not collected, which are major concerns of LTBI  
27 treatment. It is also not possible to collect specimens from individuals for genotyping tests, which  
28 are important to understand the dynamic of TB transmission. Further clinical prospective cohort  
29 studies will be necessary in order to address these LTBI research gaps. Second, completeness of  
30 an LTBI treatment is defined by the number of prescribed anti-TB drugs based on insurance claims.

1 Since adherence to the treatment cannot be assessed during the follow-up period, we hypothesized  
2 that all prescribed anti-TB drugs are taken.

3 The role of LTBI treatment on reducing TB incidence at the national level depends on the country's  
4 TB epidemiology. Although the current national initiative which aims to screen and treat LTBI in  
5 congregate settings is conducted in South Korea, scientific evidence for its effectiveness is lacking  
6 and its public health impact is still unknown. The project was carried out under South Korea's  
7 strong political will to eliminate TB disease along with the adoption of the END TB Strategy.<sup>5</sup> The  
8 WHO recently issued updated and consolidated guidelines for people with LTBI, aiming to expand  
9 testing and improve treatment; it highlighted LTBI as a key component of a comprehensive control  
10 strategy in both high and low prevalence settings.<sup>17</sup> South Korea is the first country to roll out the  
11 LTBI screening program for the general population. The result of this cohort study will identify  
12 most vulnerable populations with LTBI who will progress to active TB and help KCDC develop  
13 public health policies towards them. It will also contribute towards highlighting the importance of  
14 the LTBI program as a key component of WHO's END TB Strategy.

15



1 **Contributors**

2 Study design: JM, HWK, JPM, HWY, JUL, YL, KHK, LSS, PSJ, KSC and JSK. Funding  
3 acquisition: JSK. Manuscript drafting: JM, HWK and JSK. Critical manuscript review: HRS, ML,  
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5

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12 **Competing interests**

13 The authors declare that they have no competing interests.

14

15 **Ethics approval**

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1 **Figure legends**

2

3 Figure 1. Linkage of databases used in a prospective study of latent tuberculosis infection  
4 screening & treatment at congregate settings in South Korea

5 LTBI, latent tuberculosis infection; TB, tuberculosis; KNTSS, Korean national tuberculosis  
6 surveillance system; NHI, national health insurance; PHIS, public health information system

7

8 Figure 2. Decision tree model for latent tuberculosis infection screening program in congregate  
9 settings

10 CXR, chest x-ray; IGRA, Interferon-Gamma Release Assay; LTBI, latent tuberculosis infection;  
11 TB, tuberculosis

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1 Table 1. Key objectives of study according to follow-up periods

| <b>Follow-up Periods</b>          | <b>Key Objectives</b>                               | <b>Secondary outcomes</b>  |
|-----------------------------------|---|--|
| Short-term<br>(within 1 year)     | Prevalence of LTBI                                  | <ul style="list-style-type: none"> <li>• Difference in prevalence of tuberculosis infection among different settings</li> <li>• Risk factor of TB infection</li> <li>• Distribution of IGRA values</li> <li>• Cascade of care in LTBI</li> </ul> |
|                                   | Prevalence of active TB                             | <ul style="list-style-type: none"> <li>• Risk factors of concurrent active TB</li> </ul>   |
| Medium-term<br>(within 2~5 years) | Incidence of LTBI                                   | <ul style="list-style-type: none"> <li>• Risk factors for developing LTBI</li> </ul>   |
|                                   | Incidence of active TB                              | <ul style="list-style-type: none"> <li>• Risk factors for developing active TB</li> <li>• Efficacy of LTBI treatment on preventing active TB</li> <li>• Development of drug resistance after LTBI treatment</li> </ul>                           |
| Long-term<br>(after 10 years)     | Efficacy of LTBI screening program at country level | <ul style="list-style-type: none"> <li>• Impact on notification rate for new TB cases in general population</li> <li>• Trend of anti-TB drug resistance (INH and RIF) in general population</li> </ul>   |

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3 TB, tuberculosis; LTBI, latent tuberculosis infection; INH, isoniazid; RIF, rifampicin

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1 Table 2. Sources of database used for the prospective cohort study

| Types of database                               | Information  | Ownership  |
|---|--|--|
| LTBI screening database                         | <ul style="list-style-type: none"> <li>•Gender and age</li> <li>•Types of occupation</li> <li>•Types of congregate setting</li> <li>•Results of chest x-ray</li> <li>•Results of IGRA</li> </ul>   | Korea Centers for Disease Control and Prevention |
| National Health Information database            | <ul style="list-style-type: none"> <li>•Comorbidities</li> <li>•Socio-demographic data, including income level</li> <li>•LTBI treatment at private hospitals</li> </ul>  | National Health Insurance Service                |
| Public Healthcare Information System database   | <ul style="list-style-type: none"> <li>•LTBI treatment at public health center</li> <li>•Adverse drug reaction after LTBI treatment</li> <li>•Cause of LTBI treatment withdrawal</li> </ul>  | Public health centers                            |
| Korean National TB Surveillance System database | <ul style="list-style-type: none"> <li>•Previous TB treatment history</li> <li>•Newly notified case of active TB</li> <li>•Results of microbiological tests</li> <li>•Anti-TB treatment regimen</li> <li>•Final treatment outcome</li> </ul> | Korea Centers for Disease Control and Prevention |

2 LTBI, latent tuberculosis infection; IGRA, Interferon-Gamma Release Assay; TB- tuberculosis

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