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Unrecognized Tuberculosis: Risk Factors for Smear-Positive/Cavitary Asymptomatic Cases

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Background. Screening patients with asymptomatic active tuberculosis (TB) is crucial as they can transmit the disease. Identifying the risk factors for transmission is essential for targeted screening. Understanding how the infectiousness of asymptomatic patients with TB affects disease outcomes is crucial for developing strategies to control TB spread.

Methods. We analyzed the national Korean TB cohort data to determine the factors associated with transmission risk and clinical outcomes in patients with asymptomatic pulmonary TB. The primary outcome was the factors associated with a risk factor for transmission, while the secondary outcome was mortality in asymptomatic patients with pulmonary TB stratified by transmission risk.

Results. Among 20 455 patients with pulmonary TB, 7434 (36.4%) were asymptomatic, while 1520 (25.5%) had potential transmission risks, indicated by a positive sputum acid-fast bacillus smear test or cavitation on chest radiographs. The factors associated with a higher transmission risk included male sex (odds ratio [OR], 1.385; 95% CI, 1.172–1.636; $P < .001$), low body mass index (BMI; OR, 1.687; 95% CI, 1.420–2.004; $P < .001$), current smoking (OR, 1.443; 95% CI, 1.213–1.716; $P < .001$), diabetes (OR, 1.399; 95% CI, 1.201–1.629; $P < .001$), and autoimmune disease (OR, 2.233; 95% CI, 1.295–3.850; $P = .004$). The mortality rate was higher in patients with a risk factor for transmission risk than in those without (9.3 vs 7.1%; $P = .008$).

Conclusions. Lean, smoking men with asymptomatic TB who have DM and/or autoimmune diseases have higher transmission and mortality risk. Asymptomatic populations with these risk factors warrant targeted screening.

Keywords. asymptomatic; cohort studies; pulmonary; transmission; tuberculosis.

Respiratory symptoms in patients with pulmonary tuberculosis (TB) typically prompt pulmonary evaluation and accurate diagnosis, despite globally recognized diagnostic delays [1]. By contrast, asymptomatic individuals with active TB often remain undetected, posing transmission risks to the community and significant morbidity and mortality risks [2, 3]. Currently, active screening at the health care or community level is the only available method for identifying these individuals. Recent large-scale active screening studies indicate that up to 50% of individuals diagnosed with TB are asymptomatic [4, 5].

In South Korea, TB incidence has decreased from 70 per 100 000 in 2017 to 45 per 100 000 in 2021 [6], owing to the implementation of effective strategies for diagnosing and managing symptomatic TB. However, South Korea still experiences a higher rate of TB transmission compared with other Organization for Economic Cooperation and Development countries, likely due to undetected asymptomatic transmitters [6]. Achieving the World Health Organization's "End TB Strategy" is not feasible

Received 20 February 2025; editorial decision 14 March 2025; accepted 20 March 2025; published online 22 March 2025

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https://doi.org/10.1093/ofid/ofaf176

without addressing these silent transmitters [7]. The Korean government has considered strategies for screening close contacts of asymptomatic patients with TB, homeless individuals, prisoners, and older adult populations; however, a lack of clear evidence and guidance persists regarding the appropriate targets for asymptomatic screening [6, 8].

For Korean public health services to prioritize asymptomatic patients with TB, quantifying potential TB transmission risks in this cohort and identifying the clinical and demographic factors potentially related to TB transmission and mortality risks in different cohorts of asymptomatic patients are essential.

METHODS

Data Analysis

The Korean TB Cohort Database was established as a comprehensive multicenter prospective observational cohort study to investigate the characteristics and enhance the management of patients with TB in South Korea [9]. The database, launched in September 2018, comprised data systemically collected from patients with TB attending hospitals affiliated with the National Public–Private Mix (PPM) TB Control Project, all of whom were registered in the national TB surveillance system. According to the Korean TB treatment guidelines, the patients were monitored at set intervals throughout the anti-TB treatment period. Patients with TB who were diagnosed on days 1–10 of each month during the enrollment period were recruited for the study. During this period, trained TB specialist nurses collected data using a standardized questionnaire and case report form. The collected data were then entered into a centralized database using Microsoft Access. The regional data managers compiled monthly data from local hospitals and submitted them quarterly to the central data manager. Both regional and central data managers conducted regular audits to ensure data quality. We accessed the Korean TB cohort database from September 2018 to December 2021 and performed a secondary cross-sectional analysis of the existing "Korean TB cohort database" for asymptomatic TB patients.

Study Setting and Participants

All hospitals that participated in Korea's PPM initiative contributed to the data. South Korea, with an intermediate TB burden, has a relatively high incidence of TB compared with other high-income countries. The country's PPM TB control project, launched in 2009 and expanded nationwide by 2011, involved 210 specialized TB nurses across 127 PPM hospitals and 236 public health officials at 254 public health centers [10]. In 2022, PPM hospitals managed ~81.5% of patients with newly diagnosed TB in South Korea. The primary eligibility criterion for this analysis was a diagnosis of asymptomatic pulmonary TB, confirmed by physicians using a combination of clinical, radiographic, microbiological, and histopathological evidence to determine active TB in the absence of symptoms (cough, sputum production, shortness of breath, chest discomfort, bloody sputum, fever, fatigue, and weight loss). By contrast, patients with TB symptoms, with exclusively extrapulmonary TB, and without initial sputum samples or radiographs who could not be classified based on standard reference data were excluded.

Independent Variables

In hospitals within the PPM framework, TB specialist nurses collected the participants' demographic and clinical data through detailed interviews. The baseline data included age, sex, body mass index (BMI), household size, ethnicity, smoking status, alcohol consumption, comorbid conditions, symptoms, history of previous TB treatment, and laboratory test results. Information on the timing and results of the sputum tests, symptoms, and chest radiological findings was recorded. Based on smoking status, the participants were categorized as current, previous, or never smokers. Heavy alcohol consumption was defined as >8 weekly drinks for men and >4 drinks for women. The presence of comorbidities such as diabetes mellitus (DM) and chronic respiratory, cardiac, liver, kidney, neurological, and autoimmune diseases were recorded. We asked detailed questions about the symptoms the patients experienced using a checklist questionnaire developed by the National PPM TB Control Project that included persistent cough, sputum production, shortness of breath, chest discomfort, bloody sputum, fever, fatigue, and weight loss. TB treatment history was categorized as newly diagnosed or recurrent TB (a second episode of TB occurring following a cured first episode). According to the World Health Organization criteria, treatment outcomes were classified as treatment success, cure and completion, treatment failure, or death [11].

Assessing Transmission Risk

Considerable evidence supports the transmission risk posed by symptomatic patients with TB. Smear positivity (detectable by acid-fast bacilli [AFB] sputum smears) and cavitary pulmonary disease (observable on chest x-rays) are associated with increased disease severity and transmission [12–16]. In this large cross-sectional cohort study, we used similar measures as proxies for transmission risk and disease severity in asymptomatic patients.

Mortality

In this study, TB mortialty was defined as all-cause mortality occurring between TB diagnosis and completion of treatment. Cases were classified as TB-related or non-TB-related by physicians and TB nurse specialists. TB-related deaths were those where TB was the primary or a significant contributing cause, determined from death certificates, medical records, and the absence of other likely causes. Non-TB-related deaths were those where TB was not cited as a cause. The TB treatment outcome, including mortality, was recorded upon completion of treatment.

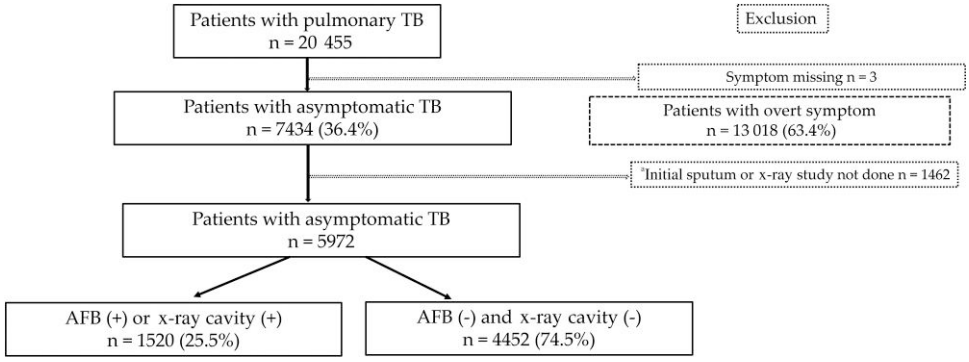

Figure 1. Flowchart. [a]Initial sputum study: sputum smear, polymerase chain reaction, culture all done. Flowchart depicting the inclusion process of patients with asymptomatic tuberculosis who were smear-positive or cavitary in the study. Abbreviations: AFB, acid-fast bacilli; TB, tuberculosis.

Outcomes

The primary goal of this study was to evaluate the risk of TB transmission and analyze treatment outcomes among asymptomatic patients. The primary outcome was the risk of transmission in asymptomatic patients with pulmonary TB, with transmission risk defined by indicators such as sputum smear positivity or cavitation on chest radiography. We aimed to identify the factors associated with an increased risk of transmission in asymptomatic patients with TB.

The secondary outcomes were the clinical outcomes of asymptomatic patients with TB, particularly mortality. These outcomes were stratified based on the level of transmission risk (eg, sputum smear positivity or cavitation on chest radiography) to assess the differences in treatment success and survival rates between patients with higher and lower transmission risks.

Statistical Analysis

Continuous data were expressed as mean values with standard deviations and analyzed using *t* tests. All variables were dichotomous. We used the conventional cutoffs of 18.5 for BMI and 65 for age. Categorical data were expressed as frequencies and percentages and assessed using Pearson's chi-square or Fisher exact tests, as appropriate. Multivariable logistic regression for factors associated with smear-positive or cavitary among individuals with asymptomatic pulmonary TB was performed with all variables with $P < .05$ in the univariable analysis. Statistical significance was set at a P value of <.05. All statistical analyses were conducted using SPSS Statistics software for Windows (version 20.0; IBM Corp., Armonk, NY, USA).

RESULTS

Proportion of Patients With Asymptomatic Pulmonary TB who Demonstrated a Transmission Risk

A total of 20 455 patients were diagnosed with PTB in South Korea from September 2018 to December 2021. After excluding 3 patients with missing symptom data, 7434 (36.4%) were initially identified to have asymptomatic pulmonary TB, while 13 018 (63.4%) presented with TB-related symptoms. Supplementary Table 1 shows the baseline characteristics comparing patients with asymptomatic and symptomatic PTB. After excluding 1462 patients without data on diagnostic tests, 5972 with asymptomatic pulmonary TB were included in the analysis. Among the asymptomatic patients included in the analysis, 1520 (25.5%) were categorized as having a transmission risk based on an operational definition (sputum AFB positivity or cavitation on chest x-ray), while 4452 (74.5%) were categorized as not having a transmission risk (sputum AFB negativity and absence of cavitation on chest x-ray) (Figure 1).

Clinical Characteristics of Patients With Asymptomatic Pulmonary TB According to Transmission Risk

Among patients with asymptomatic pulmonary TB, those with potential transmission risks (defined by sputum AFB positivity or cavitation on chest x-ray) were older (61.09 ± 16.84 vs 59.58 ± 18.30; $P < .001$), were more likely to be men (72.3% vs 63.1%; $P < .001$), and had a higher BMI (22.80 ± 59.74 vs 21.93 ± 3.23; $P < .001$). The transmission risk group also had a higher proportion of current smokers (30.3% vs 21.1%) and higher alcohol consumption (social drinkers, 33.3% vs 30.6%; heavy drinkers, 9.5% vs 6.3%; $P < .001$) compared with the low-risk group. Patients with a high transmission risk were less likely to be actively employed, cohabiting with family, or married. Patients with asymptomatic TB and a transmission risk had higher disease recurrence rates (18.9% vs 15.5%; $P = .007$) compared with those with low transmission risk. In terms of comorbidities, the prevalence of DM and autoimmune diseases was higher among patients with asymptomatic TB with a transmission risk (DM: 25.9% vs 19.8%; $P < .001$; autoimmune diseases: 1.6% vs 0.9%; $P < .001$). No significant differences were observed in the prevalence of other comorbidities (Table 1).

Table 1. Clinical Characteristics of Patients With Asymptomatic Pulmonary Tuberculosis According to Transmission Risk

Variables	Total (n = 5972)	AFB (+) or Cavity (+) (n = 1520)	AFB (–) and Cavity (–) (n = 4452)	*P* Value
Age >65 y	2274 (44.0)	584 (45.2)	1690 (43.5)	<.001
Sex (M)	3908 (65.4)	1099 (72.3)	2809 (63.1)	<.001
Low body mass index (<18.5 kg/m^2)	726 (14.1)	243 (18.9)	483 (12.5)	<.001
Smoking				<.001
Nonsmoker	3283 (55.5)	736 (48.4)	2547 (57.2)	
Ex-smoker	1288 (21.6)	322 (21.2)	966 (21.7)	
Current smoker	1399 (23.4)	461 (30.3)	938 (21.1)	
Alcohol				<.001
Never	3207 (53.7)	746 (49.1)	2461 (55.3)	
Social	1862 (31.2)	506 (33.3)	1356 (30.5)	
Heavy	424 (7.1)	144 (9.5)	280 (6.3)	
Occupation	1834 (30.7)	438 (28.8)	1396 (31.4)	.036
Cohabiting family	3795 (63.5)	922 (60.7)	2873 (75.7)	.025
Marital status	4631 (77.5)	1145 (75.3)	3486 (78.3)	.006
Registration criteria				.007
New	4992 (83.6)	1232 (81.1)	3760 (84.5)	
Recur	979 (16.4)	288 (18.9)	691 (15.5)	
Comorbidity	3585 (60)	929 (61.1)	2656 (59.7)	.432
Diabetes mellitus	1277 (21.4)	394 (25.9)	883 (19.8)	<.001
Chronic lung disease	246 (4.1)	61 (4.0)	185 (4.2)	.810
Chronic heart disease	252 (4.2)	68 (4.5)	184 (4.1)	.568
Chronic liver disease	196 (3.3)	62 (4.1)	134 (3.0)	.043
Chronic renal disease	203 (3.4)	52 (3.4)	151 (3.4)	.957
Central nervous system disease	494 (8.3)	115 (7.6)	379 (8.5)	.247
Malignancy	804 (13.5)	178 (11.7)	626 (14.1)	.020
Autoimmune disease	64 (1.1)	24 (1.6)	40 (0.9)	.026
Chest x-ray				<.001
Normal	244 (4.1)	20 (1.3)	224 (5.0)	
Suspicious of tuberculosis	3993 (66.9)	1212 (79.7)	2781 (62.5)	
Unknown	1923 (28.9)	276 (18.2)	1447 (32.5)	

Abbreviations: AFB, acid-fast bacilli; TB, tuberculosis.

Clinical Outcomes of Asymptomatic Pulmonary TB According to Transmission Risk

We analyzed clinical outcomes, focusing on the mortality rate of patients with asymptomatic pulmonary TB stratified by transmission risk. The TB-related mortality rate was higher in patients with high transmission risk than in those with low transmission risk (1.8 vs 0.8%; $P = .023$). The overall mortality rate was significantly higher in patients with high transmission risk than in those with low transmission risk (9.3% vs 7.1%; $P = .008$).

Factors Associated With Increased Transmission Risk (Smear-Positive or Cavitary) Among Individuals With Asymptomatic Pulmonary TB

The predictors of increased transmission risk among patients with asymptomatic pulmonary TB were analyzed using logistic regression. Univariate analysis revealed that male sex, BMI, active smoking status, alcohol use, active employment, cohabitation with family, recurrent TB, DM comorbidity, and autoimmune disease were factors associated with increased transmission rates. In the multivariate logistic regression, male sex (OR, 1.385; 95% CI, 1.172–1.636; $P < .001$), low BMI (OR, 1.687; 95% CI, 1.420–2.004; $P < .001$), current smoking (OR, 1.443; 95% CI, 1.213–1.716; $P < .001$), DM (OR, 1.399; 95% CI, 1.201–1.629; $P < .001$), and autoimmune disease (OR, 2.233; 95% CI, 1.295–3.850; $P = .004$) were all significant predictors of transmission risk among patients with asymptomatic pulmonary TB (Table 2). We further analyzed the factors associated with smear positivity and cavity positivity separately. The presence of cavitary lesions was associated with more factors than smear positivity (Supplementary Tables 2 and 3).

DISCUSSION

Among the 20 455 patients diagnosed with pulmonary TB in South Korea over a 40-month period, 36.4% were asymptomatic. The most surprising result of our study was that 25.5% of patients with asymptomatic TB had positive smears and/or cavitary pulmonary lesions, which are considered indicators of both severe TB pathology and high transmission risk [17]. Patients with asymptomatic TB who demonstrated positive smears and cavitary lesions had a higher TB-related mortality rate compared with those without these clinical features, which

Table 2. Factors Associated With Increased Transmission Risk Among Patients With Subclinical Tuberculosis

Risk Factors Univariate Analysis	Odds Ratio	95% CI	Multivariate Analysis		*P* Value
Age >65 y	1.071 (0.944–1.216)	.286			
Sex (M)	1.517 (1.323–1.740)	<.001	Sex (M)	1.385 (1.172–1.636)	<.001
Low body mass index (<18.5 kg/m^2)	1.517 (1.323–1.740)	<.001	Low body mass index (<18.5 kg/m^2)	1.687 (1.420–2.004)	<.001
Smoker (vs nonsmoker)					
Ex-smoker	1.126 (0.957–1.324)	.153			
Current smoker	1.665 (1.432–1.935)	<.001	Current smoker	1.443 (1.213–1.716)	< .001
Alcohol (vs non)			Alcohol (vs non)	-	
Social	1.220 (1.065–1.397)	.004	Social	-	>.05
Heavy	1.584 (1.256–1.998)	<.001	Heavy	-	>.05
Employment status	1.174 (1.023–1.348)	.022	Employment status	-	>.05
Cohabiting family	1.168 (1.023–1.334)	.022	Cohabiting family	-	>.05
Marital status	1.087 (0.923–1.279)	.316	…	…	
Registration criteria (recurrent vs new)	1.222 (1.035–1.443)	.018	Registration criteria (recurrent vs new)	-	>.05
Comorbidities	0.908 (0.797–1.033)	.142	…	…	
Diabetes mellitus	1.406 (1.211–1.633)	<.001	Diabetes mellitus	1.399 (1.201–1.629)	<.001
Chronic lung disease	0.958 (0.699–1.314)	.958	…	…	
Chronic heart disease	1.047 (0.769–1.425)	.769	…	…	
Chronic liver disease	1.283 (0.922–1.785)	.140	…	…	
Chronic renal disease	1.057 (0.753–1.482)	.749	…	…	
Central nervous system disease	0.993 (0.791–1.246)	.948	…	…	
Malignancy	0.830 (0.686–1.004)	.056	…	…	
Autoimmune disease	1.906 (1.114–3.260)	.019	Autoimmune disease	2.233 (1.295–3.850)	.004

is consistent with the findings in patients with symptomatic TB [18]. Given the high TB mortality rates and the potential for silent transmission in asymptomatic patients with positive AFB test results and/or cavitary lesions (~10% of all patients diagnosed with TB in this region), approaches focused on identifying and treating this patient group should be developed. These silent transmitters may be critical in hindering the eradication of TB in South Korea, where screening and treatment efforts are primarily focused on symptomatic patients.

In many countries, TB screening and treatment are predominantly performed in patients presenting with symptoms [19–21]. However, recent studies have demonstrated that TB infection in humans is a complex host–pathogen interaction spanning various levels of bacterial activity and immune system reactions, resulting in a spectrum of diseases ranging from dormant to active states [22]. These insights and findings from active case finding studies have shed light on the previously underappreciated clinical role of patients with asymptomatic TB [23–25]. Early symptom-free stages of TB may be as prevalent as the symptomatic form of the disease and likely play a significant role in the global morbidity and mortality of TB [26, 27]. Several recent studies have also demonstrated that the rate at which asymptomatic individuals transmit TB is comparable to that of symptomatic individuals [28]. Consequently, proactive screening measures must be developed to enhance the identification and treatment of TB in this important and often overlooked cohort [29].

Smoking, DM, and autoimmune diseases are significant risk factors for TB transmission among patients with asymptomatic TB. Previous studies have shown that smoking is a risk factor for active symptomatic TB [30, 31]. In addition, smokers are more likely to have subclinical TB, independent of age and sex, as demonstrated in a recent study [32]. Cigarette smoke exacerbates the spread and severity of TB and enhances the dispersal of bacteria into the air by affecting the mucus in the airways. Smokers might delay seeking medical aid owing to their higher tolerance for respiratory discomfort and weakened immune response, thereby increasing their vulnerability to severe but asymptomatic TB. A decreased immune response and subsequent reduction in pulmonary inflammation could contribute significantly to the high prevalence of asymptomatic disease in patients with immunological deficits.

In our study, almost 26% of asymptomatic patients with severe disease and transmission risk had DM. Previous studies have revealed that the pooled prevalence of DM is 15.3% among patients with TB [33] and that patients with DM are more likely to have symptomatic rather than asymptomatic TB [32]. However, our study showed a similar rate of DM as a comorbidity in asymptomatic and symptomatic patients (symptomatic: 20.9%; vs asymptomatic: 19.7%) (Supplementary Table 1). As TB-DM can exacerbate DM-related complications compared with DM alone and negatively impact TB treatment and outcomes, screening for TB in patients with DM using chest x-rays is essential even in the absence of symptoms [34–36].

This study has certain limitations. First, although the data were collected prospectively, the secondary analysis may have introduced bias owing to potentially missing or underreported

asymptomatic patients. Second, the TB transmission risks were assumed to be related to AFB positivity or cavitary lesions, although direct measurement of the bacterial load through mask capture could have provided a more comprehensive view [12, 13]. There is a difference between the potential ability to spread (cavitary, smear-positive) and actual spread, which includes social, behavioral, and environmental factors that influence actual TB transmission. Third, this multicenter study was only conducted in South Korea, a country with an intermediate TB burden and a high proportion of asymptomatic patients. In South Korea's unique health care system, chest x-rays are routinely performed during employment and health maintenance visits, regardless of whether the patient has or does not have symptoms, which may have led to a higher detection rate of asymptomatic TB compared with systems without routine screening; this could limit the generalizability of the findings to settings with active screening programs. The individuals with asymptomatic TB who seek care may not be representative of those who do not seek care. Fourth, the diagnosis of pulmonary TB relied on a combination of clinical, radiographic, microbiological, and histopathological evidence. Thus, some individuals classified as having "clinical TB" by clinical diagnosis only may have been misclassified. However, we did further analysis with only microbiologically diagnosed tuberculosis patients, but the factors associated with increased transmission risk or severity were the same (Supplementary Table 4). However, limited studies have addressed the risk factors of transmission in patients with asymptomatic TB, as these individuals are often regarded as noninfectious. Our findings indicate that at least one-quarter of the patients with asymptomatic TB had macroscopic and microscopic features of infectiousness, suggesting that they may be transmitting the disease. Smoking and conditions that impair the immune system, such as DM and autoimmune diseases, complicate the early identification of TB symptoms despite the ongoing transmission risks due to severe disease. Additionally, smoking and immuno-compromised status are predictors of TB severity and can result in poor TB outcomes. Given the risk posed by undetected TB to individuals and the community, more emphasis should be placed on actively screening and identifying individuals with and without symptoms.

CONCLUSIONS

Lean men with asymptomatic TB who are current smokers or have DM and/or autoimmune diseases are at an increased risk of transmitting TB. Furthermore, asymptomatic patients with a transmission risk have a higher TB-related mortality rate than those without a transmission risk. Thus, TB screening should also target asymptomatic populations with current smoking, DM, and autoimmune diseases to enhance early TB detection and control.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors have read and agreed to the published version of the manuscript.

Ethical approval. The Korean Disease Control and Prevention Agency has the authority to hold and analyze surveillance data for public health and research purposes. The Korea Disease Control and Prevention Agency approved the use of data and provided them without including personal identification information. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Inje University Ilsan Paik Hospital (No. ISPAIK 2021-08-012) and the Institutional Review Board of the Catholic University of Korea (No. C19ONDI0458), which waived the need for informed consent as no patients were at risk.

Financial support. This study was supported by the National Health Promotion Fund, which is funded by the Korea Disease Control and Prevention Agency, Republic of Korea.

Potential conflicts of interest. T.C.R. receives funding support from FIND through a service contract with UC San Diego. T.C.R. receives grant funding from the National Institutes of Health and US Dept of Defense to develop and evaluate TB diagnostics. T.C.R. is a co-founder, board member, and unpaid shareholder of Verus Diagnostics Inc. Verus Diagnostics had no role in the design or implementation of the study. T.C.R. is a co-inventor on patents pertaining to drug-resistant TB. The terms of this arrangement were reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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