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Nationwide coverage of molecular drug susceptibility testing in patients with pulmonary multidrug/rifampicin-resistant tuberculosis in South Korea: a retrospective cohort study (2015–2021)

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ABSTRACT

Background We assessed the coverage of molecular drug susceptibility testing (mDST) among patients with pulmonary multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) in South Korea and identified factors influencing the lack of mDST implementation.

Methods This retrospective study included patients with pulmonary MDR/RR-TB who initiated tuberculosis (TB) treatment between January 2015 and September 2021. Data were obtained from the K-TB-N cohort, an integrated national TB database linking three datasets. We assessed mDST coverage, temporal trends and factors associated with the lack of mDST implementation. mDST was defined as the use of the Xpert MTB/RIF assay or line probe assay (LPA) for isoniazid and rifampicin (first-line LPA).

Results In total, 4637 patients were included in the analysis. Of the 4637 patients, 1342 (28.9%) did not undergo mDST; whereas, 3295 (71.1%) underwent mDST. Over the study period, a statistically significant annual increase in mDST coverage was observed, escalating from 49.1% in 2015 to 96.9% in 2021 ($p<0.001$). Throughout the study, the coverage of the Xpert MTB/RIF assay remained lower than that of LPA (22.1% vs 64.2%, $p<0.001$). Multivariable logistic regression analysis identified several factors independently associated with a decreased likelihood of mDST being conducted, including TB treatment initiation in secondary general hospitals, small hospitals or primary clinics, as well as in non-public-private mix (PPM) participating institutions. In addition, transfers between PPM-participating and non-participating institutions during the treatment period and sputum acid-fast bacilli smear-negative status were significantly associated with lower mDST uptake.

Conclusion Although the increasing mDST coverage is a positive development, further efforts are needed to achieve nationwide and universal implementation, particularly for the Xpert MTB/RIF assay, in South Korea.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Wide implementation of molecular drug susceptibility testing (mDST) is recommended for the rapid diagnosis and treatment of patients with multidrug/rifampicin-resistant tuberculosis. However, data on the coverage of mDST and the factors influencing its lack of implementation remain limited.

WHAT THIS STUDY ADDS

⇒ The implementation of mDST in South Korea has been increasing; however, the use of the Xpert MTB/RIF assay remains suboptimal. Several factors associated with the lack of mDST implementation were also identified.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clarification of the current status and trends in mDST coverage, along with identification of factors associated with its non-implementation, may inform improvements to the national tuberculosis control programme.

INTRODUCTION

Tuberculosis (TB) remains one of the most critical respiratory infectious diseases, posing a serious threat to global public health. In 2023, an estimated 10.8 million individuals developed TB worldwide.[1] During the same year, TB accounted for approximately 1.25 million deaths, ranking among the leading causes of mortality from a single infectious agent.[1] These persistently high incidence and mortality rates are in stark contrast with the targets set by the WHO under the End TB Strategy. Furthermore, the emergence of multidrug-resistant and rifampicin-resistant TB (MDR/RR-TB) continues to undermine global TB control efforts. In 2023, an estimated 400 000 individuals developed MDR/RR-TB; however, only 40% of these cases were diagnosed and initiated on appropriate treatment, yielding a treatment success rate of only 68%.[1]

Rapid diagnosis and appropriate treatment of MDR/RR-TB are essential for improving patient outcomes, mitigating the development of further drug resistance and preventing the transmission of resistant strains within the community.[2–4] Traditionally, culture-based phenotypic drug susceptibility testing (pDST) has been considered the gold standard diagnostic modality for drug-resistant TB. However, the protracted growth kinetics of *Mycobacterium tuberculosis* impede the rapid detection of drug resistance and the initiation of timely treatment.[5 6] Conversely, molecular DST (mDST), which identifies mutations in resistance-associated genes, enables more rapid detection of drug resistance compared with pDST.[7] The MTBDRplus line probe assay (LPA) (Hain Lifescience, Nehren, Germany) and Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA) have been endorsed by the WHO for the rapid diagnosis of MDR/RR-TB. Currently, the WHO recommends the Xpert MTB/RIF assay as the initial diagnostic test for TB and rifampicin resistance in adults with signs and symptoms of pulmonary TB, rather than smear microscopy, culture or pDST.[8 9]

With the increasing use of mDST for MDR/RR-TB in diverse clinical settings, its association with rapid diagnosis, timely treatment initiation and improved patient outcomes remains well established.[10–18] In addition, the WHO emphasises the importance of universal access to varied mDST methodologies for the prompt detection of MDR/RR-TB.[8 9] However, data on mDST coverage in South Korea remain limited. We assessed mDST coverage among patients with pulmonary MDR/RR-TB in South Korea and identified factors influencing the lack of mDST implementation.

METHODS

Study design and population

This retrospective cohort study was conducted in South Korea, where the TB notification rates for new patients were 63.2 and 35.7 per 100 000 population in 2015 and 2021, respectively.[19] In 2023, MDR/RR-TB was estimated to affect 2.9% of newly diagnosed patients and 8.5% of previously treated patients in South Korea.[1] The study population was derived from the Korea Disease Control and Prevention Agency - Tuberculosis - National Health Insurance Service (K-TB-N) cohort, an integrated national database of TB patients created by linking three sources: the Korea Tuberculosis Surveillance System (KTB-Surv), established by the Korea Disease Control and Prevention Agency, which contains TB notification data from 2011 to 2021; the National Health Information Database, maintained by the National Health Insurance Service (NHIS), which includes healthcare data from 2002 to 2021; and the Causes of Death Statistics Korea database, which provides mortality data from 2011 to 2021. We included TB patients from the K-TB-N cohort who were diagnosed with MDR/RR-TB based on DST findings recorded in KTB-Surv between 2011 and 2021. Patients who initiated treatment before 2015 were excluded due to insufficient DST information, and those who began treatment after September 2021 were excluded due to incomplete data on mDST implementation. In addition, patients diagnosed exclusively with extrapulmonary TB and those with missing or erroneous data were excluded. Furthermore, patients who received treatment at public health centres were excluded due to insufficient data from the NHIS (figure 1). The Institutional Review Board of the Yonsei University Health System (approval number: 4-2022-0595) and the Korea National Health Insurance Service Medical Request Review Committee (NHIS-2022-1-737) approved the study protocol. Because only de-identified data were used in this study, the requirement for informed consent was waived by the review board.

Measurement and definition

The following data were extracted from the database: gender, age, comorbidities, previous TB treatment history, sputum acid-fast bacilli (AFB) smear results, household income level and the year of TB treatment initiation. TB treatment history was categorised as follows: new patients were those who had never received TB treatment or had taken anti-TB drugs for <1 month; whereas, previously treated patients were those who had received anti-TB drugs for ≥1 month.[20] Geographic regions were classified into four categories, based on the regional divisions of South Korea, determined by the administrative area of residence at the time of TB treatment initiation. Healthcare institutions were categorised according to their size and participation in the public-private mix (PPM) TB control project, based on the facility where treatment was first initiated. In terms of PPM participation, patients who were transferred between PPM-participating and non-participating institutions during treatment were classified as 'mix'. mDST included the Xpert MTB/RIF assay or LPA for isoniazid and rifampicin (first-line LPA). The performance of mDST was defined as the administration of these tests within 3 months before or after TB treatment initiation at the same institution where treatment was initiated.

Guidelines for the use of mDST in South Korea

In South Korea, LPA and the Xpert MTB/RIF assay were introduced in 2007 and 2012, respectively, and have since been incorporated into standard clinical practice.[18] The 2014 South Korean TB guidelines recommended selective mDST for patients exhibiting a high risk of drug-resistant TB, such as those undergoing retreatment or those with severe TB or HIV infection.[21] In the revised 2017 guidelines, these indications were sustained, with the added provision that mDST could be considered for other patient groups.[22] However, since the 2020 guideline revision, mDST has been recommended for all suspected or confirmed TB patients.[23] In South Korea, all costs associated with the diagnosis of drug resistance and the treatment of TB have been provided without charge since 2016.

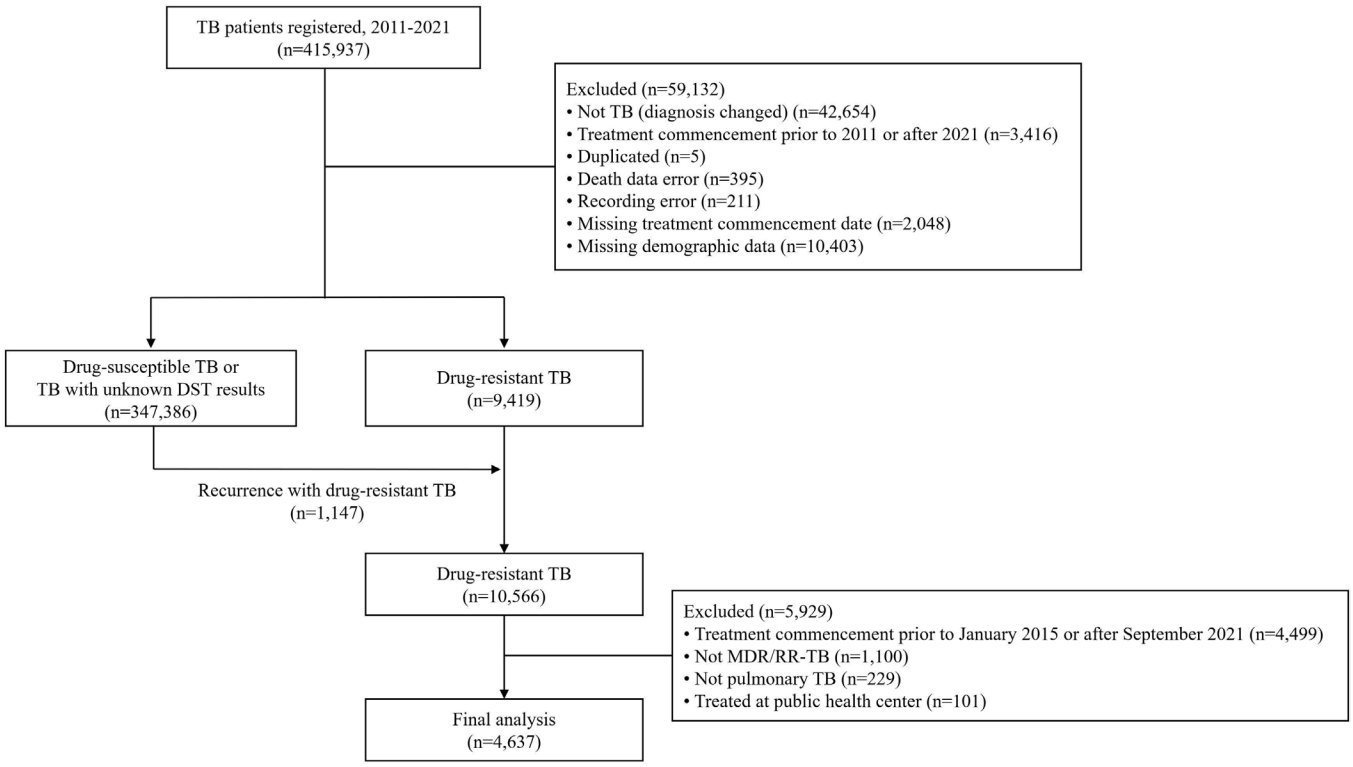

Figure 1 Flowchart of study participants. DST, drug susceptibility test; MDR, multidrug-resistant; RR, rifampicin-resistant; TB, tuberculosis.

Statistical analysis

A descriptive analysis was conducted to assess the distribution of individual covariates in relation to the performance of mDST. Continuous variables are presented as mean±SD for normally distributed data, and comparisons were performed using the Student's t-test. For non-normally distributed data, variables are expressed as medians and IQR, and the Mann–Whitney U test was used for comparisons. Categorical variables are presented as frequencies and percentages, with comparisons conducted using the χ^2 test. To evaluate the factors influencing mDST implementation, a multivariable logistic regression analysis was performed to estimate ORs and 95% CIs. In addition, trends in mDST coverage were analysed for the overall study population and stratified based on previous TB treatment history, institution type, participation in the PPM project, and region. Statistical analyses were performed using the SAS Enterprise Guide (version 7.1; SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics of participants

Among the 415 937 TB patients registered in the K-TB-N cohort between 2011 and 2021, 4637 with pulmonary MDR/RR-TB were included in the final analysis based on the predefined inclusion and exclusion criteria (figure 1). The median age of the participants was 54.0 (IQR 39.0–67.0) years, with 68.2% (n=3163) being male. Regarding TB treatment history, 35.8% (n=1662) had undergone previous TB treatment, and 50.3% (n=2333) were positive for AFB smears. The predominant institution type initiating TB treatment was secondary general hospitals (45.7%, n=2120), and 62.2% (n=2882) of patients received treatment at institutions participating in the PPM project (table 1).

Of the 4637 patients, 1342 (28.9%) did not undergo mDST; whereas, 3295 (71.1%) underwent mDST. compared with the non-mDST group, patients in the mDST group were older and had a higher prevalence of comorbidities, including diabetes, malignancy, HIV infection and steroid use. Furthermore, a greater proportion of patients in the mDST group initiated treatment at tertiary general hospitals and PPM-participating institutions compared with the non-mDST group (table 1).

mDST coverage and trends

Figure 2 illustrates the annual mDST coverage for all patients from 2015 to 2021. The overall mDST coverage was 71.1%, demonstrating a significant increasing trend over the years (p<0.001): 49.1% in 2015, 50.6% in 2016, 55.4% in 2017, 90.0% in 2018, 92.3% in 2019, 94.8% in 2020 and 96.9% in 2021. This upward trend was consistently observed in new and previously treated patients, as well as for the Xpert MTB/RIF assay and LPA (online supplemental table S1 and figures S1 and S2). However, throughout the entire study period, the coverage of the Xpert MTB/RIF assay was consistently lower than that of LPA, across the total patient population (22.1% vs

Table 1 Comparison of patients who underwent molecular drug susceptibility testing and those who did not

	Total (n=4637)	Patients who did not undergo mDST (n=1342)	Patients who underwent mDST (n=3295)	P value*
Gender, male	3163 (68.2)	899 (67.0)	2264 (68.7)	0.254
Age, year	54.0 (39.0–67.0)	51.0 (31.0–64.0)	55.0 (41.0–68.0)	<0.001
Region				0.076
Seoul, Incheon and Gyeonggi-do	2417 (52.1)	716 (53.4)	1701 (51.6)	
Daejeon, Sejong, Chungcheong-do and Gangwon-do	496 (10.7)	161 (12.0)	335 (10.2)	
Busan, Ulsan, Daegu and Gyeongsang-do	1184 (25.5)	322 (24.0)	862 (26.2)	
Gwangju, Jeju and Jeolla-do	540 (11.6)	143 (10.7)	397 (12.0)	
Household income level				0.050
5 (highest)	784 (16.9)	206 (15.4)	578 (17.5)	
4	840 (18.1)	223 (16.6)	617 (18.7)	
3	910 (19.6)	290 (21.6)	620 (18.8)	
2	839 (18.1)	238 (17.7)	601 (18.2)	
1	826 (17.8)	258 (19.2)	568 (17.2)	
0 (lowest)	438 (9.4)	127 (9.5)	311 (9.4)	
Type of institution†				<0.001
Tertiary general hospital	1539 (33.2)	279 (20.8)	1260 (38.2)	
Secondary general hospital	2120 (45.7)	603 (44.9)	1517 (46.0)	
Small hospital	530 (11.4)	230 (17.1)	300 (9.1)	
Primary clinic	181 (3.9)	128 (9.5)	53 (1.6)	
Long-term care hospital	32 (0.7)	5 (0.4)	27 (0.8)	
Type of institution, PPM participating				<0.001
PPM participating	2882 (62.2)	584 (43.5)	2298 (69.7)	
PPM non-participating	221 (4.8)	121 (9.0)	100 (3.0)	
Mix‡	1534 (33.1)	637 (47.5)	897 (27.2)	
Previous treatment history of TB				0.203
New	2921 (63.0)	853 (63.6)	2068 (62.8)	
Previously treated	1662 (35.8)	468 (34.9)	1194 (36.2)	
Unknown	54 (1.2)	21 (1.6)	33 (1.0)	
Sputum AFB smear, positive	2333 (50.3)	647 (48.2)	1686 (51.2)	0.068
Comorbidity				
Diabetes	1434 (30.9)	380 (28.3)	1054 (32.0)	0.014
Malignancy	456 (9.8)	81 (6.0)	375 (11.4)	<0.001
HIV	12 (0.3)	0 (0.0)	12 (0.4)	0.024
Organ transplantation	5 (0.1)	1 (0.1)	4 (0.1)	>0.999
Treatment with steroid	382 (8.2)	85 (6.3)	297 (9.0)	0.003
Treatment with TNF inhibitor	12 (0.3)	1 (0.1)	11 (0.3)	0.199
TB treatment year				<0.001
2015	859 (18.5)	437 (32.6)	422 (12.8)	
2016	856 (18.5)	423 (31.5)	433 (13.1)	
2017	733 (15.8)	327 (24.4)	406 (12.3)	
2018	693 (14.9)	69 (5.1)	624 (18.9)	
2019	640 (13.8)	49 (3.7)	591 (17.9)	

Continued

Table 1 Continued

	Total (n=4637)	Patients who did not undergo mDST (n=1342)	Patients who underwent mDST (n=3295)	P value*
2020	501 (10.8)	26 (1.9)	475 (14.4)	
2021	355 (7.7)	11 (0.8)	344 (10.4)	

Data are presented as the number (percentage) or the median (IQR).
*Comparison between patients who underwent molecular drug susceptibility testing and those who did not.
†n=4402 (excluding 235 patients with missing data on institution type; patients who did not undergo mDST: n=1245, patients who underwent mDST: n=3157).
‡Transfer between PPM-participating and non-participating institutions during the treatment period.
AFB, acid-fast bacilli; mDST, molecular drug susceptibility test; PPM, public-private mix; TB, tuberculosis; TNF, tumour necrosis factor.

64.2%), new patients (23.5% vs 64.8%) and previously treated patients (19.9% vs 63.5%) (online supplemental table S1 and figures S1 and S2).

Throughout the study period, mDST coverage was 81.9% in tertiary general hospitals, 71.6% in secondary general hospitals and 51.1% in small hospitals, primary clinics and long-term care hospitals. Although all institution types exhibited an increasing trend in coverage over time, mDST coverage in small hospitals, primary clinics and long-term care hospitals remained at 71.0% in 2021 (figure 3 and online supplemental table S2). Regarding PPM participation, mDST coverage was 79.7% in PPM-participating institutions, compared with 45.3% in non-participating institutions throughout the study period. Despite this gap, both groups demonstrated an increasing trend in coverage throughout the study (figure 3 and online supplemental table S2). Furthermore, all four regions exhibited an upward trend in mDST coverage over the study period (online supplemental figure S3 and table S2).

Factors affecting mDST conduct

Table 2 presents the factors associated with carrying out mDST. In the multivariable logistic regression analysis, TB treatment initiation between 2017 and 2021 was significantly associated with an increased likelihood of mDST conduct. Conversely, TB treatment initiation in

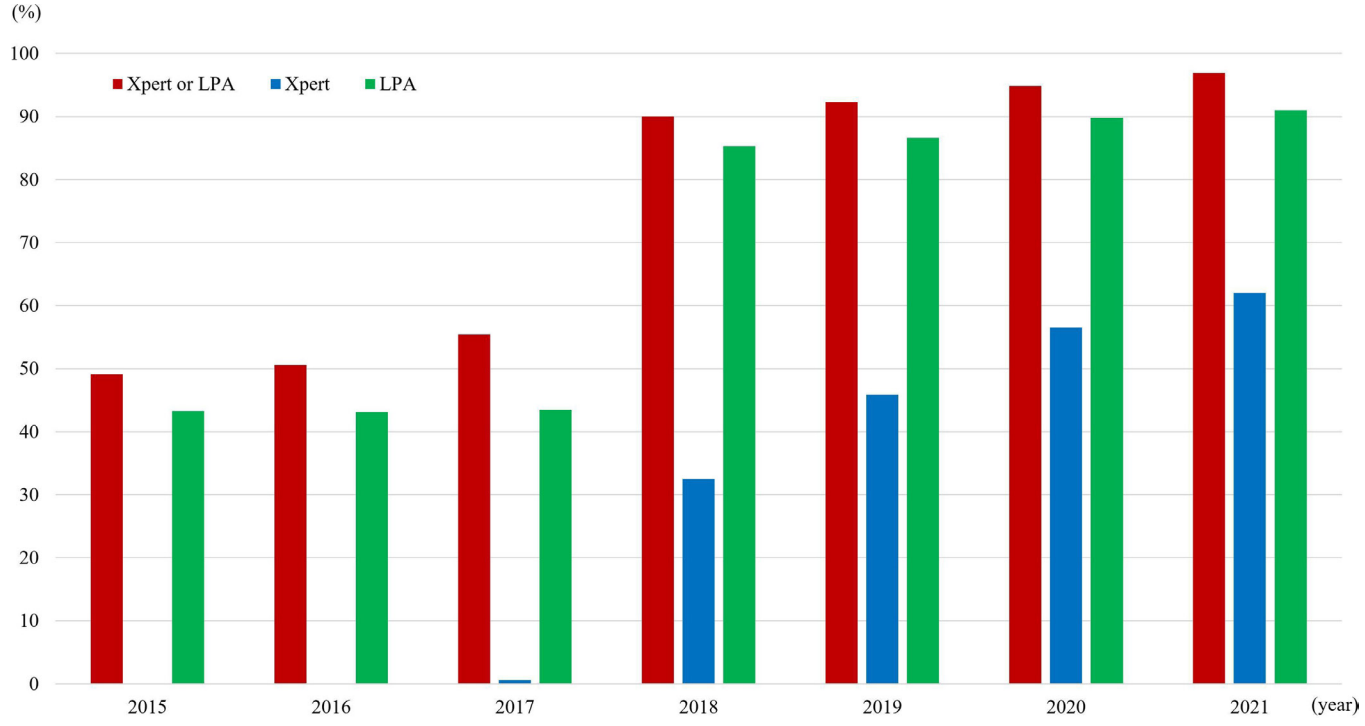

Figure 2 Coverage of molecular drug susceptibility testing among patients with pulmonary multidrug/rifampicin-resistant tuberculosis. Data are presented as the number of molecular drug susceptibility tests conducted out of the total number of patients (%); total number of patients (n=4637). All three groups exhibited a significant increasing trend (p<0.001). LPA, line probe assay; Xpert, Xpert MTB/RIF assay.

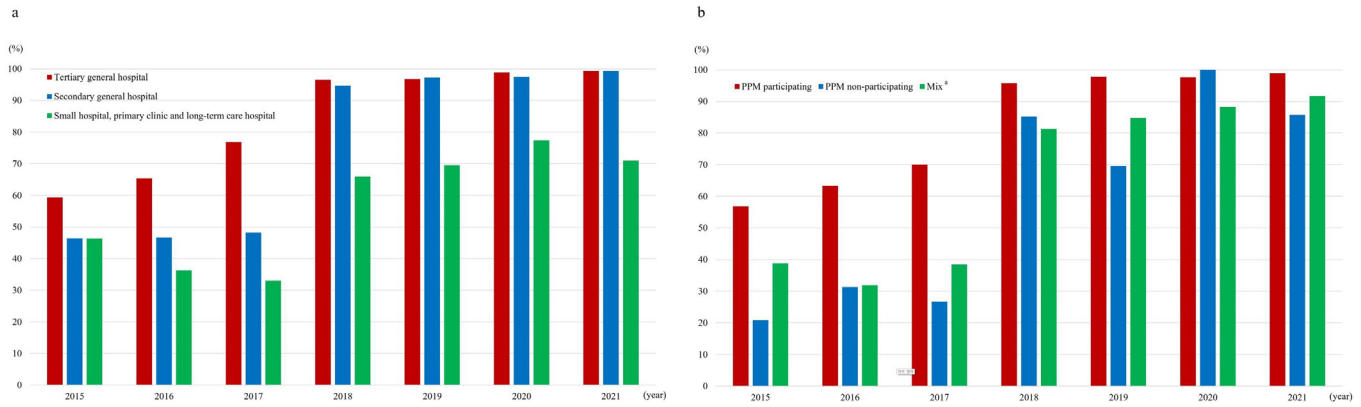

Figure 3 Coverage of molecular drug susceptibility testing among patients with pulmonary multidrug/rifampicin-resistant tuberculosis by institution type and participation in the public-private mix tuberculosis control project. (a) Coverage by institution type (n=4402). (b) Coverage by participation in the public-private mix tuberculosis control project (n=4637). Data are presented as the number of molecular drug susceptibility tests (Xpert MTB/RIF assay or line probe assay) conducted out of the total number of patients (%). A significant increasing trend was observed across all groups in (a) and (b) (p<0.001). [a]Transfer between PPM-participating and non-participating institutions during the treatment period. PPM, public-private mix.

secondary general hospitals, small hospitals, primary clinics and PPM non-participating institutions, as well as transfers between PPM-participating and non-participating institutions during the treatment period and AFB smear-negative status were associated with a decreased probability of mDST conduct.

DISCUSSION

Despite the progressive global adoption of mDST, a significant proportion of patients with MDR/RR-TB remain undiagnosed. In 2023, only 79% of individuals with bacteriologically confirmed pulmonary TB underwent testing for rifampicin resistance worldwide.[1] The identification of factors associated with the lack of mDST implementation is crucial for optimising patient management and strengthening TB control programmes across different countries.

In our study, mDST coverage in South Korea exhibited an increasing trend over the study period across the overall population and various subgroups. This improvement can be attributed to the progressive changes in TB guidelines over time, as well as the implementation of policies ensuring cost-free TB diagnosis and treatment. However, we identified several factors associated with the lack of mDST implementation, including TB treatment initiation in secondary general hospitals, small hospitals, primary clinics and PPM non-participating institutions, and patients with AFB smear-negative results. In our study, nearly two-thirds of patients were new cases. This finding suggests that the transmission of drug-resistant *M. tuberculosis* in the community remains inadequately controlled, emphasising the need for rapid mDST-based diagnosis to facilitate timely patient management.[24 25]

Previous studies have identified several factors contributing to the lack of mDST implementation, including fear or stigma associated with positive results among patients or healthcare providers, the cost of testing, challenges related to sputum collection and transport, the location of TB lesions and HIV infection.[26 27] However, these factors may vary depending on the prevalence of drug-resistant TB and the resources available in each country, emphasising the need for a country-specific approach. In our study, treatment initiation in secondary general hospitals, small hospitals and primary clinics was identified as a factor associated with the lack of mDST implementation compared with tertiary general hospitals. Notably, mDST coverage in small hospitals and primary clinics remained at approximately 71% even in 2021. Similar trends have been reported in previous studies from South Korea; in addition, an Indian study demonstrated that mDST coverage varies by healthcare facility type.[18 26 28] The lower coverage in smaller healthcare facilities is likely to be attributable to a lack of necessary equipment, trained personnel and formal laboratory processes required for mDST. However, in South Korea, an extensive network of commercial laboratories, an efficient specimen transport system and a free-of-charge policy minimise logistical and financial barriers to testing. Conversely, the lower mDST coverage in these institutions is primarily attributable to a lack of knowledge among healthcare providers, particularly as TB patients in such settings are often first seen by non-specialists. Similarly, for PPM non-participating institutions, which are predominantly smaller facilities, inadequate mDST coverage can be ascribed to the same challenges.

To address these challenges, regular and systematic education programmes and promotional activities are essential for healthcare providers across diverse healthcare settings. Although South Korea currently implements TB education programmes for healthcare providers, these initiatives primarily focus on personnel in PPM-participating institutions, MDR/RR-TB specialised centres, or large hospitals. Greater attention and proactive measures are required to extend TB education

Table 2 Factors affecting molecular drug susceptibility testing

	Univariate		Multivariate	
	OR	95% CI	aOR	95% CI
Male gender	1.082	0.945 to 1.239	1.101	0.921 to 1.316
Age, group, year				
<20	Reference		Reference	
20–29	1.051	0.628 to 1.756	1.400	0.736 to 2.662
30–39	1.224	0.737 to 2.034	1.382	0.732 to 2.607
40–49	1.461	0.883 to 2.418	1.485	0.788 to 2.796
50–59	1.437	0.873 to 2.365	1.465	0.780 to 2.751
60–69	1.976	1.187 to 3.289	1.483	0.777 to 2.830
70–79	1.785	1.065 to 2.989	1.549	0.805 to 2.982
>80	2.116	1.251 to 3.578	1.550	0.793 to 3.027
Region				
Seoul, Incheon and Gyeonggi-do	Reference		Reference	
Daejeon, Sejong, Chungcheong-do and Gangwon-do	0.876	0.712 to 1.078	0.797	0.614 to 1.036
Busan, Ulsan, Daegu and Gyeongsang-do	1.127	0.965 to 1.316	1.119	0.919 to 1.363
Gwangju, Jeju and Jeolla-do	1.169	0.947 to 1.442	1.109	0.850 to 1.447
Household income level				
5 (highest)	Reference		Reference	
4	0.986	0.791 to 1.230	0.969	0.734 to 1.280
3	0.762	0.617 to 0.941	1.044	0.799 to 1.364
2	0.900	0.723 to 1.120	1.266	0.957 to 1.674
1	0.785	0.632 to 0.974	1.009	0.764 to 1.333
0 (lowest)	0.873	0.673 to 1.133	1.163	0.832 to 1.625
Type of institution				
Tertiary general hospital	Reference		Reference	
Secondary general hospital	0.557	0.475 to 0.654	0.572	0.472 to 0.692
Small hospital	0.289	0.233 to 0.358	0.383	0.292 to 0.502
Primary clinic	0.092	0.065 to 0.130	0.082	0.052 to 0.129
Long-term care hospital	1.196	0.456 to 3.132	1.083	0.349 to 3.360
Type of institution, PPM participating				
PPM participating	Reference		Reference	
PPM non-participating	0.210	0.159 to 0.278	0.338	0.232 to 0.494
Mix*	0.358	0.312 to 0.410	0.385	0.320 to 0.462
Previous TB treatment	1.052	0.921 to 1.202	1.173	0.989 to 1.391
Sputum AFB smear, negative†	0.888	0.782 to 1.009	0.554	0.469 to 0.655
Diabetes	1.191	1.036 to 1.369	1.085	0.898 to 1.311
Malignancy	1.999	1.559 to 2.565	1.211	0.891 to 1.646
Organ transplantation	1.629	0.182 to 14.576	0.707	0.066 to 7.608
Treatment with steroid	1.465	1.141 to 1.881	1.147	0.830 to 1.587
Treatment with TNF inhibitor	4.479	0.579 to 36.640	4.993	0.539 to 46.287
TB treatment year				
2015	Reference		Reference	
2016	1.060	0.877 to 1.281	1.056	0.853 to 1.306
2017	1.286	1.055 to 1.567	1.308	1.046 to 1.636
2018	9.365	7.061 to 12.420	13.813	9.985 to 19.107

Continued

Table 2 Continued

	Univariate		Multivariate	
	OR	95% CI	aOR	95% CI
2019	12.490	9.064 to 17.211	19.118	13.150 to 27.793
2020	18.919	12.470 to 28.702	26.762	16.601 to 43.143
2021	32.384	17.507 to 59.902	30.300	15.985 to 57.434

In total, 4402 patients were included in the analyses (excluding 235 patients with missing data on institution type).
*Transfer between PPM-participating and non-participating institutions during the treatment period.
†Includes cases where testing was not performed or results were unknown (n=43).
AFB, acid-fast bacilli; aOR, adjusted OR; PPM, public-private mix; TB, tuberculosis; TNF, tumour necrosis factor.

to community hospitals and primary care clinics. Alternatively, referring suspected TB patients to institutions equipped to provide specialised TB care may be a viable strategy. As of 2024, 139 institutions in South Korea participate in the PPM project, while 64 institutions serve as designated MDR/RR-TB specialised centres under the MDR-TB consortium project. These specialised facilities play a critical role in the rapid diagnosis and management of drug-resistant TB. However, to facilitate the timely referral of suspected TB cases and ensure prompt diagnosis and treatment, additional administrative support, regulatory oversight and structured coordination may be necessary. Therefore, the Health Insurance Review and Assessment Service in South Korea conduct routine quality assessments of institutions managing TB patients, with mDST coverage recently incorporated as an evaluation criterion. The introduction of appropriate incentives for institutions that demonstrate high-quality TB management could further enhance mDST coverage and improve overall TB care outcomes.

In our study, although mDST coverage exhibited an overall increasing trend, the coverage of the Xpert MTB/RIF assay for the entire population in 2021 remained at 62.0%, significantly lower than the 91.0% coverage of LPA in the same year. This finding indicates that the diagnosis of MDR/RR-TB in South Korea continues to favour LPA over the Xpert MTB/RIF assay. This preference may stem from the earlier introduction of LPA, which has led to greater familiarity among healthcare providers and broader integration into the healthcare system. However, in cases of low bacillary burden, the Xpert MTB/RIF assay exhibits higher sensitivity than LPA and plays a crucial role in detecting rifampicin resistance.[10 29] In our study, the AFB smear-negative rate among all patients reached 50%, and smear negativity was associated with reduced mDST implementation. This is likely to be due to the inability to perform LPA on smear-negative specimens during the early stages of TB diagnosis. Considering these limitations, the Xpert MTB/RIF assay should be prioritised as the initial test for detecting rifampicin resistance rather than LPA in South Korea. Rifampicin resistance serves as a reliable proxy for MDR-TB, and the WHO and South Korean TB guidelines recommend the same treatment regimens for RR-TB and MDR-TB.[23 30]

Several additional considerations are essential for improving the diagnosis of MDR/RR-TB in South Korea. Rapid mDST for quinolones remains limited in availability, despite the critical role of quinolone resistance in determining appropriate treatment regimens for MDR/RR-TB. Expanding access to rapid diagnostic tools, including the Xpert MTB/XDR assay and second-line LPA, is imperative. Furthermore, the development and implementation of mDST for new and repurposed anti-TB drugs are urgently needed. The revised WHO and South Korean TB guidelines recommend various shorter regimens for MDR/RR-TB treatment, such as the 'BPaL(M)', '9-month all-oral' and 'MDR-END' regimens, rather than the traditional longer regimen.[23 30 31] However, rapid mDST for key drugs in these regimens, such as bedaquiline, delamanid, pretomanid and linezolid, remains commercially unavailable. An additional critical consideration is the translation of rapid MDR/RR-TB diagnosis into timely treatment initiation. A previous study in South Korea revealed that, in numerous cases, despite the detection of rifampicin resistance via mDST, second-line drugs for MDR/RR-TB were not commenced until pDST results were obtained.[18] Therefore, targeted educational interventions are essential to ensure healthcare providers promptly apply mDST results to clinical decision-making.

Our study has several limitations. First, the retrospective design inherently carries the potential for missing data or inaccuracies in medical records. However, the primary dataset used, KTB-Surv, is recognised for its high level of completeness.[32] Second, the generalisability of our findings is limited, as mDST coverage should be assessed in the context of each country's TB burden, the prevalence of drug-resistant TB and available healthcare resources. Third, our study lacked sufficient data on the proportion of patients who initiated empirical TB treatment prior to an MDR/RR-TB diagnosis and on the timing of MDR/RR-TB diagnosis after treatment initiation. In cases where MDR/RR-TB diagnosis was delayed following the initiation of empirical treatment, reductions in bacterial burden and symptoms may have hindered the provision of adequate sputum samples for additional mDST, which could in turn have affected the observed mDST coverage. Lastly, for a more accurate assessment and analysis of

mDST coverage, it would be preferable to include all TB patients, regardless of drug resistance, for whom mDST was recommended according to the guidelines in each period. However, due to limitations of the database used, it was not possible to specifically identify patients who were recommended for mDST under the respective guidelines.

Despite these limitations, our study is significant as the first nationwide, large-scale analysis of mDST coverage and the factors contributing to it not being conducted in South Korea, an intermediate TB burden, high-income country. The observed increase in mDST coverage is encouraging; however, further efforts are needed to achieve nationwide and universal adoption, particularly of the Xpert MTB/RIF assay. Strengthening mDST implementation will be critical for improving patient outcomes and mitigating the transmission of drug-resistant TB in South Korea.

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