Journal of Microbiology, Immunology and Infection 55 (2022) 917—925

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Temporal trends of pharmacologic treatments for tuberculosis and multidrug resistant tuberculosis following dissemination of treatment guidelines in South Korea

Han Eol Jeong [a,f], Junyeong Choi [a], In-Sun Oh [a,f], Hyunjin Son [b], Seung Hun Jang [c], Sun-Young Jung [d], Ju-Young Shin [e,f,*]

[a] *School of Pharmacy, Sungkyunkwan University, Suwon 16419, South Korea*
[b] *Department of Preventive Medicine, College of Medicine, Dong-A University, Busan 49201, South Korea*
[c] *Division of Pulmonary, Allergy, and Critical Care Medicine, College of Medicine, Hallym University Sacred Heart Hospital, Hallym University, Anyang 14068, South Korea*
[d] *College of Pharmacy, Chung-Ang University, Seoul 06974, South Korea*
[e] *Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Seoul 06355, South Korea*
[f] *Department of Biohealth Regulatory Science, Sungkyunkwan University, Suwon 16149, South Korea*

Received 29 October 2020; received in revised form 25 May 2021; accepted 20 November 2021
Available online 30 November 2021

KEYWORDS
Multidrug resistant tuberculosis;
Nationwide study;
Prescription patterns;
Time series;
Tuberculosis

Abstract *Background/Purpose(s):* The World Health Organization (WHO) released treatment guidelines for multidrug resistant tuberculosis (MDR-TB) in 2008, with subsequent revisions in 2011; Korea disseminated corresponding guidelines in 2011 and 2014, respectively. Thus, we aimed to investigate the temporal trends of and the updated guideline's impact on the prescription patterns of anti-TB drugs.
Methods: We conducted a time-series study using Korea's nationwide healthcare database (2007—2015), where patients with TB or MDR-TB were included. Only anti-TB drugs prescribed during the intensive phase of treatment for TB (two months) or MDR-TB (eight months) were assessed. We estimated the annual utilization of TB treatment regimens and the relative difference (RD) in the proportion of MDR-TB treatment medications between the following periods: before the first Korean guideline (June 2008 to March 2011); between the first and

* Corresponding author. School of Pharmacy, Sungkyunkwan University, 2066, Seobu-ro, Jangan-gu, Suwon, Gyeonggi-do, 16419, South Korea.
E-mail address: shin.jy@skku.edu (J.-Y. Shin).

https://doi.org/10.1016/j.jmii.2021.11.007

revised guidelines (April 2011 to July 2014); after the revised guideline (August 2014 to December 2015).
Results: Of 3523 TB (mean age 54.1 years; male 56.8%) patients, treatment regimens for TB complied with guideline recommendations as >80% of patients received either quadruple (mean 66.8%) or triple (14.5%) therapy of first-line anti-TB drugs. Following the WHO's guideline update, prescription patterns changed accordingly among 111 MDR-TB (mean age 46.0 years; male 67.6%) patients, as use of pyrazinamide (RD +20.3%) and prothionamide (+11.5%) increased (recommended to be compulsory), and streptomycin (−43.1%) decreased (ototoxicity risks).
Conclusions: Anti-TB drug prescription patterns for both TB and MDR-TB well reflected WHO's treatment guideline as well as corresponding domestic guidelines of South Korea.

Introduction

Tuberculosis (TB) remains an unresolved global issue, with the World Health Organization (WHO) reporting an approximate estimate of 10.0 million TB patients in 2018.[1] It is common clinical practice to use multiple anti-TB drugs to treat TB, where treatment regimens may differ depending on the treatment phase (intensive or continued).[2] This two-part course of treatment has set place as the standard mainly due to the risks of developing drug resistance. Thus, making appropriate prescriptions is highly important in successfully treating TB.[3] Moreover, healthcare providers should be well aware of the most recent treatment guidelines for TB in order to prescribe appropriate treatment regimens.

South Korea, despite having high standards of healthcare, is the only country among the Organization for Economic Cooperation and Development nations with high incidence rates of TB (77 per 100,000 in 2016).[4] From 1966 to 2005, the Korea Academy of Tuberculosis and Respiratory diseases released TB treatment guidelines four times (1966, 1990, 1997, 2005) to help clinicians treat TB patients. Subsequently, to control and eventually eradicate TB in Korea, the Korea Centers for Disease Control and Prevention (KCDC) disseminated a more comprehensive TB treatment guideline in 2011, followed by a revision in 2014 that reflected the WHO guideline amendments.[5,6] Treatment for TB remained consistent in both editions, as use of quadruple or triple therapy of first-line anti-TB drugs (isoniazid [H], rifampicin [R], ethambutol [E], pyrazinamide [Z]) were recommended for use during the intensive phase of treatment. However, guidelines for multidrug resistant TB (MDR-TB) were amended to five agents (Z, fluoroquinolone, injectable agent, prothionamide, cycloserine) from four agents (injectable agent, fluoroquinolone, two from E or Z, group 4 or 5 anti-TB drugs). Although few previous studies have described prescription patterns of anti-TB drugs, no published evidence to our knowledge has examined the change in prescription patterns of anti-TB drugs following the update of treatment guidelines.[7,8]

Therefore, we aimed to describe the temporal prescription patterns of TB treatments and to investigate the impact of TB treatment guidelines disseminated by the WHO and KCDC on clinical practice in treating MDR-TB.

Methods

Data source

We used the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database of South Korea from January 1, 2002 to December 31, 2015, which contains healthcare utilization information from a randomly extracted 2.2% sample of the entire Korea population of 50 million; the NHIS-NSC database contains approximately one million individuals. The NHIS-NSC database provides data on sociodemographic characteristics such as sex, age, region of residence, and socioeconomic status (health insurance type and income level) as well as information on prescribed drugs, procedures, and diagnoses based on the International Classification of Disease, 10th revision (ICD-10) codes. In 1983, the South Korean government implemented the relieved co-payment policy for patients with rare or incurable diseases by reducing their amount of co-payment to lessen their economic burden and has expanded the policy coverage largely since 2005.[9] Accordingly, patients eligible for this policy are given specific codes (relieved co-payment policy codes) along with their corresponding healthcare utilization information; these codes are also available in the NHIS-NSC database. As the aforementioned policy codes are used for reimbursement purposes, they are considered to have higher accuracy and validity over diagnosis codes.[10]

Study Designs

We applied two different study designs to complete our study objectives. First, we assessed the prescription pattern of TB (excluding MDR-TB) treatment for the entire study period (January 1, 2011 to December 31, 2015), as treatment recommendations for TB remained consistent between the two guidelines. Second, we investigated the impact of treatment guidelines on the prescription pattern of MDR-TB treatment for the study period divided into three periods as follows: 1) before dissemination of the first guideline (June 1, 2008 to March 31, 2011); 2) after the first guideline but before dissemination of the second guideline

(April 1, 2011 to July 31, 2014), and 3) after dissemination of the second guideline (August 1, 2014 to December 31, 2015); which revised recommendations for MDR-TB treatment. A visual representation for the above-mentioned study objectives are displayed in Fig. 1.

Study population

The inclusion and exclusion criteria of study patients are shown in Fig. 2. We identified all patients with TB or MDR-TB by using the relieved co-payment policy codes. Beneficiaries of the relieved co-payment policy for MDR-TB were classified as "V206" since June 1, 2007, while those for TB other than MDR-TB (ICD-10: A15-A19) were classified as "V246" starting January 1, 2010. We excluded the following patients: 1) records of "V246" any time before 2010, as this classification code was first introduced in 2010; 2) patients with MDR-TB who had "V206" but were not diagnosed with MDR-TB (ICD-10: U84.3), as they are considered to be false positive patients; and 3) anti-TB drug prescriptions accompanied with records of "V206" between June 1, 2007 and May 31, 2008, or "V246" between January 1, 2010 and December 31, 2010, to restrict to incident patients with TB or MDR-TB.

Eligible prescriptions for assessment

Treatment guidelines for both TB and MDR-TB have outlined a more detailed recommendation of anti-TB medications during the intensive phase of treatment compared to the continuation phase. Therefore, only anti-TB drugs prescribed during the intensive phase of treatment for TB (first two months) and MDR-TB (first eight months) were eligible for assessment. Among the prescriptions during the intensive phase of treatment, prescriptions that contained only one injectable anti-TB drug were excluded to prevent overestimation of the total number of prescriptions.

Statistical analysis

The number and proportion for categorial variables and the mean and standard deviation for continuous variables were calculated to describe the baseline sociodemographic

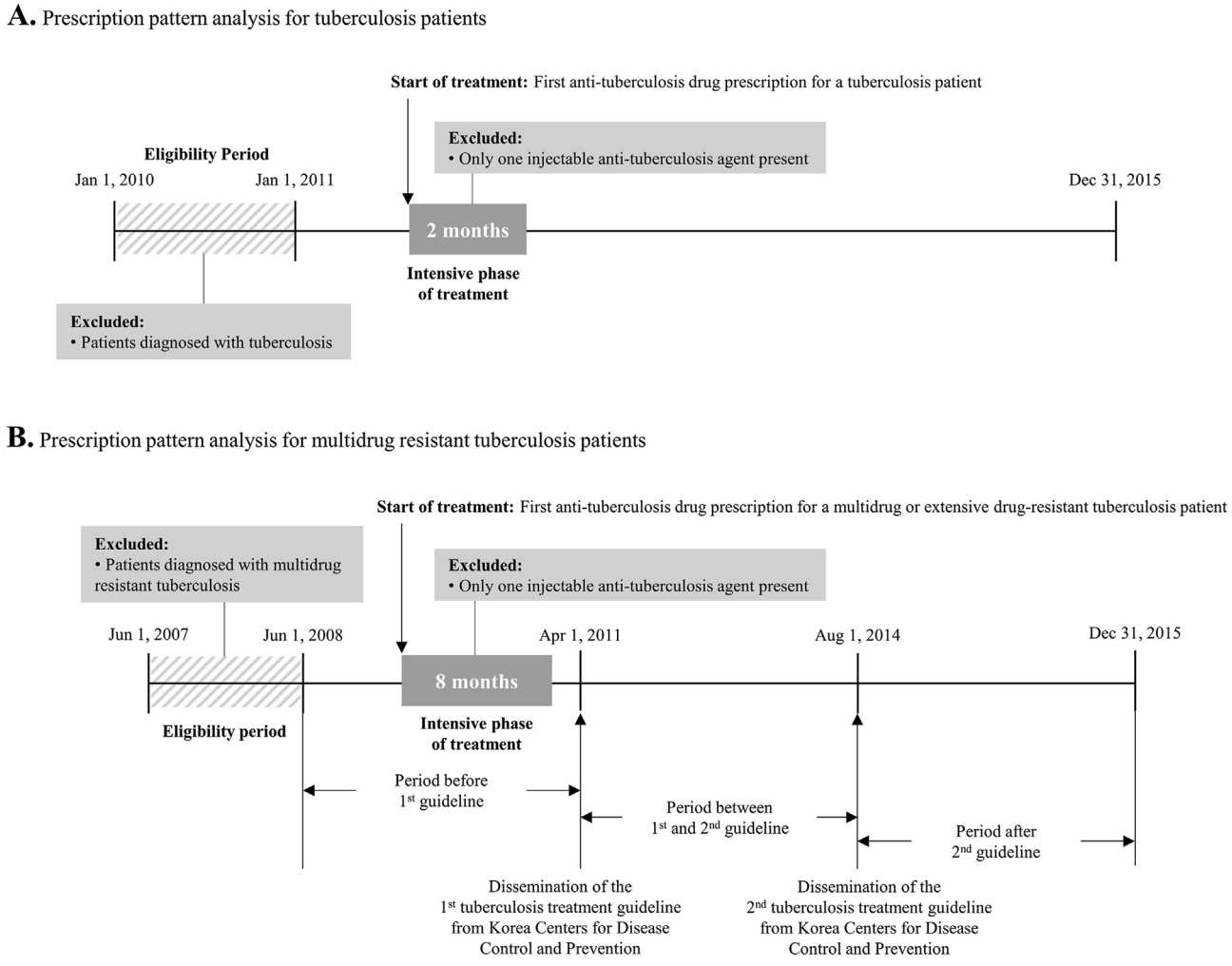


Figure 1. Study diagram demonstrating the eligible prescriptions and study period of prescription pattern analyses for (A) tuberculosis patients and (B) multi-drug resistant tuberculosis patients.

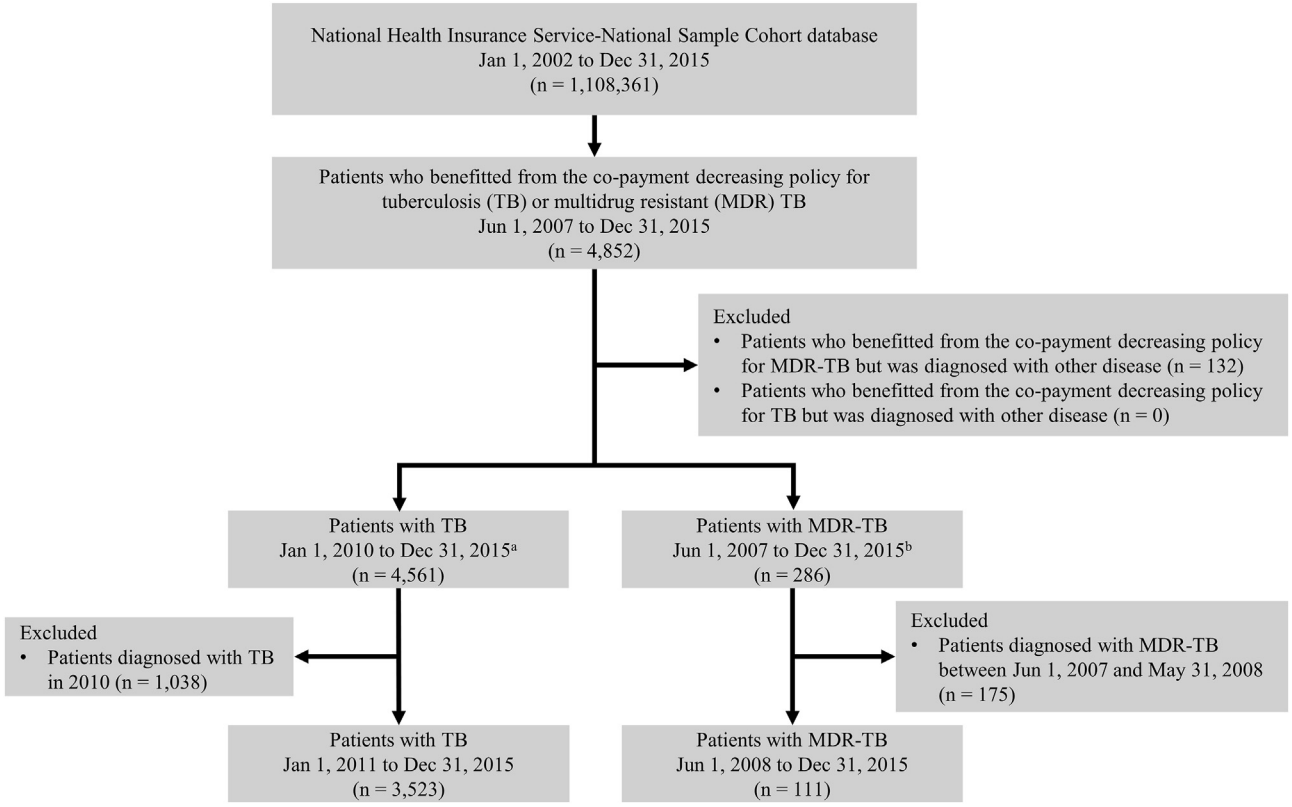


Figure 2. Flow diagram showing the study inclusion and exclusion criteria. [a] Patients with tuberculosis can be detected from January 1, 2010 because the relieved co-payment policy code for tuberculosis was introduced on January 1, 2010. [b] Patients with multidrug resistant tuberculosis can be detected from June 1, 2007 because the relieved co-payment policy code for multidrug resistant tuberculosis was introduced on June 1, 2007.

characteristics of patients with TB and MDR-TB. The absolute standardized difference (aSD) was estimated to determine imbalances present between the two patient groups, where aSD$\geq$0.1 denoted an important imbalance.

For TB treatments, we estimated the annual proportion of each treatment regimen of first-line oral anti-TB drugs by dividing the number of prescriptions for the respective regimen over the total number of prescriptions in each year. The annual proportions were estimated from 2011 to 2015. Meanwhile, for treatments of MDR-TB, we estimated the absolute difference (AD) with 95% confidence intervals (CIs) for the proportion of each treatment medication between the three periods, by subtracting the proportion of periods 1 and 2 from that of periods 2 and 3, respectively. We also estimated the relative difference (RD) with 95% CIs by dividing the estimated AD over the proportion of the previous period and multiplied by 100. For instance, the AD between period 1 and 2 was calculated as the proportion of period 1 subtracted from the proportion of period 2, while the corresponding RD was calculated as dividing this AD by the proportion of period 1 and then multiplied by 100.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and the study protocol was approved by the Institutional Review Board of Sungkyunkwan University (IRB No. SKKU 2019-10-030-001) and obtaining informed consent was waived by the Institutional Review Board.

Results

We identified a total of 3523 and 111 patients with TB and MDR-TB, respectively (Fig. 2). Baseline socioeconomic characteristics revealed that, as compared with MDR-TB patients, TB patients were older (mean age 54.1 years [standard deviation 20.1] versus 46.0 [19.0]; aSD 0.404) and had less males (56.8% versus 67.6%; aSD 0.223). Although there were no important imbalances (aSD$<$0.1) present in health insurance type or income level between TB and MDR-TB patients, significant imbalances were found in the region of residence with a lower proportion of TB patients residing in metropolitan areas or cities (88.7% versus 92.0%; aSD 0.114) than MDR-TB patients (Table 1).

From 2011 to 2015, prescription patterns of treatment regimens for TB were consistent with the KCDC treatment guidelines, which are based on WHO's recommendations, throughout the years (Fig. 3). Of all prescription of first-line anti-TB drugs (H, R, E, Z) during the intensive phase of TB treatment, the most common treatment regimen was quadruple therapy (HREZ), ranging from 65.3% to 69.8% in our study period. Although the second common regimen was triple therapy of HRE (10.3% to 13.9%), use of first-line anti-TB drugs with other drugs was found to be the third most common treatment regimen (11.1% to 12.2%). Nevertheless, use of either quadruple or triple therapy of first-line anti-TB drugs remained the most prevalent treatment regimen for TB.

Table 1 Baseline characteristics of patients with tuberculosis or multidrug resistant tuberculosis in South Korea.

	Tuberculosis[a] (n = 3523)	MDR-Tuberculosis (n = 111)	aSD
Sex (n, %)			0.223
Male	2001 (56.8)	75 (67.6)	
Female	1522 (43.2)	36 (32.4)	
Age (years; mean ± STD)	54.1 ± 20.1	46.0 ± 19.0	
Age group (years; n, %)			0.404
<19	91 (2.6)	4 (3.6)	
19-44	1114 (31.6)	54 (48.7)	
45-64	1068 (30.3)	30 (27.0)	
≥65	1250 (35.5)	23 (20.7)	
Health insurance type (n, %)			0.008[c]
National health insurance	3370 (95.7)	106 (95.5)	
Medical aid	153 (4.3)	5 (4.5)	
Income level[b] (n, %)			0.093[c]
Low	710 (20.2)	24 (21.6)	
Lower-Middle	935 (26.5)	27 (24.3)	
Upper-Middle	1032 (29.3)	36 (32.4)	
High	846 (24.0)	24 (21.6)	
Region of residence (n, %)			0.114
Metropolitan	1600 (45.4)	51 (46.0)	
Cities	1521 (43.2)	51 (46.0)	
Provinces	402 (11.4)	9 (8.1)	

[a] Tuberculosis patients and does not include patients with MDR-tuberculosis.
[b] Income levels are classified into 11 groups ranging from 0 to 10, according to the type of health insurance. 10 of the groups are for employee and district subscribers while, group 0 indicates medical aid. Low (groups 0–2), Lower-Middle (groups 3–5), Upper-Middle (groups 6–8), High (groups 9–10).
[c] aSD≥0.1 denotes an important imbalance.
Abbreviations: aSD, absolute standardized difference; MDR, multidrug resistant; STD, standard deviation.

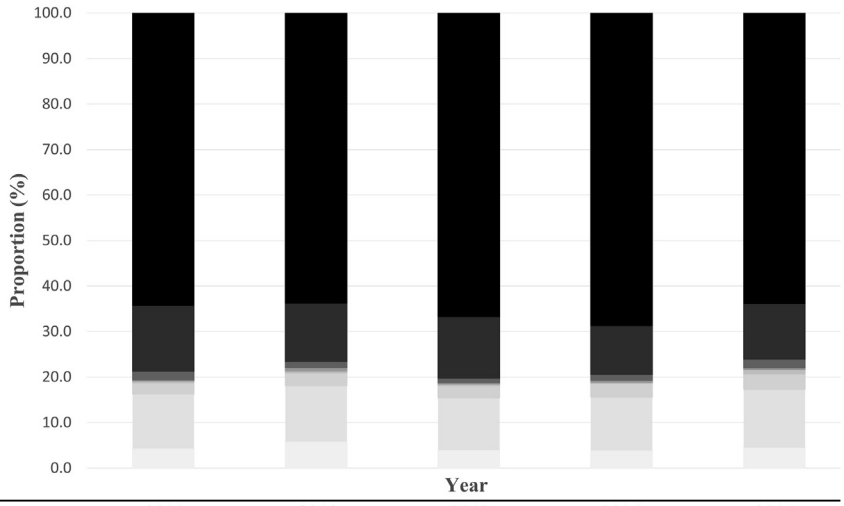
Upon dissemination of the first treatment guideline for TB in Korea (April 2011), the pattern of MDR-TB treatments followed guideline recommendations with prescriptions of E (RD 23.7%, 95% CI + 16.0% to +35.2%), Z (+104.5%, +71.6% to +152.7%), kanamycin (+24.1%, +16.6 to +34.9%) increased and ofloxacin (−96.1%, −725.9% to −12.7%), para-aminosalicylic acid (PAS) (−36.5%, −52.7% to −25.4%), and all group 5 drugs decreased. Likewise, with release of the revised guideline for MDR-TB in August 2014, prescription patterns changed accordingly as follows: use of Z (+20.2%, +10.7% to +38.3%) and prothionamide (+11.5%, +5.8% to +22.6%) increased as they were now recommended to be compulsory, while streptomycin (−43.1%, −106.1% to −17.7%) decreased as the guideline did not recommend it due to the common occurrence of resistance and ototoxicity. In general, treatment regimens for MDR-TB changed over time by adhering to treatment guideline recommendations of the KCDC (Table 2).

Discussion

Findings from this study demonstrate that treatment regimens for both TB and MDR-TB were consistent to clinical guidelines released by the WHO and their corresponding versions disseminated by the KCDC. Most patients with TB received either quadruple or triple therapy of first-line anti-TB drugs throughout our study period, which are recommendations suggested by treatment guidelines. Similar findings were also observed for MDR-TB, as appropriate adjustments to treatment regimens were made following the release or update of guidelines for MDR-TB treatment. Thus, this is the first nationwide study to have shown that utilization patterns of anti-TB drugs for TB and MDR-TB complied well with global and domestic recommendations and further, showed that healthcare providers had high adherence to them.

Despite being an indirect comparison, findings from both our study (based on number of prescriptions; 66.8%) and a study conducted in Yunnan, China (based on number of patients; 74.8%), reported that HREZ quadruple therapy accounted for approximately 70%.[8] However, unlike quadruple therapy, the proportion for triple therapy was different between the two studies as the proportion of South Korea (14.5%) was approximately three-fold compared to that of China (4.6%). Meanwhile, another study conducted in Taiwan (incidence per 100,000 persons of TB[11] [43.9] and MDR-TB[12] [0.46] in 2016) found that of new TB cases, only one in two patients received HREZ quadruple therapy (53.3%) during their intensive phase of treatment, a proportion smaller than those of South Korea[4] (TB [60.4] and MDR-TB [1.7]) and China[13] (TB [63.7] and MDR-TB [5.2]).[7] On the contrary, patients from Taiwan received the highest proportion of triple therapy (26.0%) when compared to South Korea (14.5%) and China (4.6%). The observed differences between Taiwan and South Korea may be attributed to Taiwan's clinical guidelines that allowed for physicians to modify treatment regimens when deemed necessary, which were mainly based on their clinical experiences.

A study conducted from the Beijing Chest Hospital between 2011 and 2015 found analogous results to those of our study as Z, levofloxacin, and moxifloxacin were three of the most commonly prescribed anti-TB drugs among MDR-TB patients.[14] In contrast to what was expected among group 4 treatments based on the WHO guideline in 2011, which recommended prothionamide and cycloserine or PAS only when cycloserine was inappropriate, PAS was found to be the most prescribed agent in the Beijing study. However, we observed that PAS was the least prescribed drug amongst the group 4 agents. In assuming that the respective healthcare providers of each country treated their patients with MDR-TB based on the identical treatment guideline disseminated by the WHO, we believe such



Anti-tuberculosis regimens	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	2015 n (%)
Total prescriptions	1,996 (100.0)	2,255 (100.0)	2,115 (100.0)	1,930 (100.0)	1,807 (100.0)
HREZ	1,309 (65.6)	1,477 (65.5)	1,435 (67.8)	1,347 (69.8)	1,180 (65.3)
HRE	277 (13.9)	273 (12.1)	273 (12.9)	198 (10.3)	211 (11.7)
HRZ	36 (1.8)	29 (1.3)	21 (1.0)	24 (1.2)	34 (1.9)
HEZ	6 (0.3)	15 (0.7)	6 (0.3)	9 (0.5)	6 (0.3)
REZ	7 (0.4)	9 (0.4)	7 (0.3)	4 (0.2)	15 (0.8)
≤2 first-line[a] drugs	47 (2.4)	59 (2.6)	54 (2.6)	55 (2.8)	59 (3.3)
First-line drugs + Others	229 (11.5)	260 (11.5)	234 (11.1)	217 (11.2)	221 (12.2)
Others without first-line drugs	85 (4.3)	133 (5.9)	85 (4.0)	76 (3.9)	81 (4.5)

Figure 3. Yearly proportion of anti-tuberculosis regimens by possible combinations for tuberculosis (excluding multidrug resistant tuberculosis) patients from 2011 to 2015. Abbreviation: H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide. [a] First-line drugs are isoniazid, rifampicin, ethambutol and pyrazinamide.

discrepancy in prescriptions are likely due to their interpretation and health care status.

We found prescribing patterns that were consistent with both global and domestic treatment guidelines of TB. However, for TB patients, there were a few prescriptions that contained only second-line anti-TB drugs (3.9—5.9%), with no first-line anti-TB drugs. Most of these cases could be considered as those who experienced adverse events upon using first-line anti-TB drugs and therefore, could no longer be treated with any of them. Furthermore, although cycloserine was more and more strongly recommended for MDR-TB patients over time, a conflicting temporal pattern was observed with its proportion decreasing with time. This observed decrease of cycloserine may be due to healthcare providers in South Korea opting to prescribe prothionamide over cycloserine among the group 4 anti-TB drugs; accordingly, prescriptions of prothionamide increased with time. In addition to group 4 drugs, fluoroquinolones have been also recognized as essential in treating MDR-TB. One study showed the superiority of levofloxacin over ofloxacin in TB treatment, while other studies have reported equivalence of levofloxacin and moxifloxacin.[15—17] The results of our study are in line with these studies in that both levofloxacin and moxifloxacin were more commonly prescribed over ofloxacin. As for injectable agents (kanamycin, amikacin, streptomycin, capreomycin), as all these agents have relatively similar efficacy and adverse event profiles, there would be no particular rationale to use more than one injectable agent in treating MDR-TB.[18—20] Yet, streptomycin is no longer a preferred injectable agent owing to its low reliability from susceptibility tests and common occurrence of developing resistance to H-resistant TB, which includes MDR-TB.[21,22] Moreover, as amikacin is administered intravenously and capreomycin has been registered in the Korea Orphan & Essential Drug Center of South Korea, prescription of these drugs is limited. Hence, kanamycin had become the most preferred injectable agent for MDR-TB in Korea up until treatment guidelines have revised their recommendations in a way that they no longer recommend injectable agents in treating MDR-TB. In support, kanamycin was the most prescribed injectable agent and there were no prescriptions for capreomycin in our study.

Recent global and domestic treatment guidelines for TB have made significant revisions, especially for the recommended treatment regimen for MDR-TB, in order to reflect newly developed treatment options of bedaquiline and delamanid.[23,24] Upon such amendments, anti-TB drugs of levofloxacin or moxifloxacin, bedaquiline, and linezolid are currently the most recommended and preferred treatments for MDR-TB. To examine whether these novel updates in treatment guidelines are well-adhered to in actual clinical practice, this warrants further investigations that utilize more recent data.

Strengths of this study are that, to our knowledge, this is the first population-based study that used nationwide claims data of South Korea to have examined the temporal trends in the prevalence of treatments for both TB and MDR-TB. As the NHIS-NSC database underwent rigorous systematic stratified random sampling from all Koreans, our

Table 2 Proportion of anti-tuberculosis drugs prescribed for multidrug resistant tuberculosis, before and after the dissemination of the 1st and 2nd editions of the Korean tuberculosis treatment guidelines.

	Period 1[a]	Period 2[b]	Period 3[c]	Difference between Periods 1 and 2 % (95% confidence interval)		Difference between Periods 2 and 3% (95% confidence interval)	
	n (%)	n (%)	n (%)	Absolute	Relative	Absolute	Relative
Total number of prescriptions	206 (100.0)	293 (100.0)	66 (100.0)	N/A	N/A	N/A	N/A
Group 1 (First-line oral anti-tuberculosis agents)							
Ethambutol	54 (26.2)	95 (32.4)	22 (33.3)	6.2 (−1.8 to 14.3)	23.7 (16.0—35.2)	0.9 (−11.7 to 13.5)	2.8 (1.6—5.0)
Pyrazinamide	66 (32.0)	192 (65.5)	52 (78.8)	33.5 (25.1—41.9)	104.5 (71.6—152.7)	13.3 (2.0—24.5)	20.2 (10.7—38.3)
Group 2 (Injectable anti-tuberculosis drugs)							
Kanamycin	68 (33.0)	120 (41.0)	36 (54.6)	7.9 (−0.6 to 16.5)	24.1 (16.6—34.9)	13.6 (0.32—26.9)	33.2 (19.4—56.8)
Amikacin	4 (1.9)	16 (5.5)	2 (3.0)	3.5 (0.3—6.7)	181.2 (59.7—550.2)	−2.4 (−7.3 to 2.5)	−44.5 (−198.5 to −10.0)
Streptomycin	50 (24.3)	47 (16.0)	6 (9.1)	−8.2 (−15.4 to −1.0)	−33.9 (−53.0 to −21.7)	−7.0 (−15.1 to 1.2)	−43.1 (−106.1 to −17.7)
Capreomycin	0 (0.0)	0 (0.0)	0 (0.0)	0	N/A	0	N/A
Group 3 (Fluoroquinolone)							
Levofloxacin	113 (54.9)	105 (35.8)	23 (34.9)	−19.0 (−27.8 to −10.3)	−34.7 (−49.9 to −24.1)	−1.0 (−13.7 to 11.8)	−2.8 (−4.8 to −1.6)
Moxifloxacin	61 (29.6)	164 (56.0)	38 (57.6)	26.4 (17.9—34.8)	89.2 (61.0—130.0)	1.6 (−11.6 to 14.8)	2.9 (1.7—4.9)
Ofloxacin	18 (8.7)	1 (0.3)	0 (0.0)	−8.4 (−12.3 to −4.5)	−96.1 (−725.9 to −12.7)	−0.3 (−1.0 to 0.3)	−100.0
Group 4 (Second-line oral anti-tuberculosis agents)							
para-aminosalicylic acid	123 (59.7)	111 (37.9)	12 (18.2)	−21.8 (−30.5 to −13.1)	−36.5 (−52.7 to −25.4)	−19.7 (−30.5 to −8.9)	−52.0 (−101.5 to −26.7)
Cycloserine	185 (89.8)	247 (84.3)	43 (65.2)	−5.5 (−11.4 to 0.4)	−6.1 (−10.6 to −3.5)	−19.1 (−31.4 to −6.9)	−22.7 (−41.2 to −12.5)
Prothionamide	149 (72.3)	215 (73.4)	54 (81.8)	1.1 (−6.9 to 9.0)	1.5 (1.0—2.2)	8.4 (−2.2 to 19.0)	11.5 (5.8—22.6)
Group 5 (Other anti-tuberculosis agents)							
Amoxicillin/clavulanate	28 (13.6)	30 (10.2)	5 (7.6)	−3.4 (−9.2 to 2.5)	−25.0 (−42.7 to −14.3)	−2.7 (−9.9 to 4.6)	−26.0 (−69.8 to −9.7)
Clarithromycin	14 (6.8)	4 (1.4)	0 (0.0)	−5.4 (−9.1 to −1.8)	−79.4 (−246.4 to −25.9)	−1.4 (−2.7 to 0.0)	−100.0
Linezolid	0 (0.0)	1 (0.3)	0 (0.0)	0.3 (−0.3 to 1.0)	N/A	−0.3 (−1.0 to 0.3)	−100.0

[a] Period before the dissemination of the 1st edition of the Korean tuberculosis treatment guideline (Jun 1, 2008 to Mar 31, 2011).
[b] Period after the dissemination of the 1st edition of the Korean tuberculosis treatment guideline and before 2nd edition of the Korean tuberculosis treatment guideline (Apr 1, 2011 to Jul 31, 2014).
[c] Period after the dissemination of the 2nd edition of the Korean tuberculosis treatment guideline (Aug 1, 2014 to Dec 31, 2015).
Abbreviation: N/A, not applicable.

results are likely to be a robust representation of general Korean population. Second, with the fee-for-service reimbursement system utilized in South Korea, we were able to include both inpatient and outpatient prescription records of anti-TB treatments and thereby, minimizing exposure misclassification.

However, our study also has limitations. First, patients included in our study may not be incident cases of TB despite

excluding all patients with a prescription record of anti-TB drugs in the first one year of study period. With the median time to TB relapse reported as 12 months, recurrent TB cases who developed TB relapse after more than 12 months may have been included in our study and we may have misclassified them as an incident cases.[25] Second, we did not consider dosages of the prescribed drugs as our interest was the type of drug prescribed in assessing adherence to treatment guidelines. Third, treatment regimens are likely to have been different in treating particular TB patients, such as those with low liver or renal functions or human immunodeficiency virus (HIV) infection. However, as information on liver and renal function and HIV infection were either unavailable or had low validity in the database used in this study, we were unable to classify patients depending on the aforementioned criteria.[26–28] Fourth, we were unable to determine if patients with TB or MDR-TB truly adhered to their respective treatments as the NHIS-NSC database used in this study does not provide information on drug adherence. However, as patients with TB or MDR-TB receive close monitoring and intensive care during the recommended initial course of treatment, it can be assumed that these patients adhered well to their prescribed medications. Lastly, other interventions besides the treatment guidelines released by the WHO and the KCDC could have influenced the clinical practice of healthcare providers. However, as we observed real-world prescription patterns that were largely in line with guideline recommendations, we expect those influences to be minimal in our study.

In summary, prescription patterns of anti-TB drugs for patients with TB or MDR-TB in South Korea showed high compliance to treatment guidelines disseminated by the WHO. It would be interesting for future investigators to assess the drug utilization patterns of anti-TB drugs in other TB-prevalent countries and communities to determine the underlying association between adherence to guidelines and rates of treatment success or adverse events. While awaiting results of confirmatory studies, healthcare providers should follow clinical guidelines for the treatment of TB and MDR-TB.

Funding

This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, South Korea [grant number: HI19C1233] and a grant from Ministry of Food and Drug Safety, South Korea in 2021-2025 [grant number: 21153MFDS607].

Data availability

The health insurance claims database of the National Health Insurance Service can be accessed at: https://nhiss.nhis.or.kr/bd/ab/bdaba022eng.do.

Declaration of competing interest

All authors declare no conflicts of interest.

Acknowledgments

We thank the National Health Insurance Service of South Korea for providing the National Health Insurance Service-National Sample Cohort database.

References

1. World Health Organization (WHO). *Global tuberculosis report*. Available at: https://www.who.int/tb/publications/global_report/en/, 2019. [Accessed 10 July 2020].
2. World Health Organization (WHO). *Treatment of tuberculosis: guidelines — Fourth edition*. Available at: https://apps.who.int/medicinedocs/en/m/abstract/Js21646en/. [Accessed 6 July 2020].
3. Shah NS, Auld SC, Brust JCM, Mathema B, Ismail N, Moodley P, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. *N Engl J Med* 2017;**376**:243–53.
4. Go U, Park M, Kim U-N, Lee S, Han S, Lee J, et al. Tuberculosis prevention and care in Korea: evolution of policy and practice. *J Clin Tuberc Other Mycobact Dis* 2018;**11**:28–36.
5. Korea Centers for Disease Control and Prevention (KCDC). *Korean guidelines for tuberculosis first edition*. Available at: http://www.kslm.org/rang_board/inc/download.php?code=all_notice&num=199, 2011. [Accessed 9 July 2020].
6. Korea Centers for Disease Control and Prevention (KCDC). *Korean guidelines for tuberculosis second edition*. Available at: https://www.cdc.go.kr/board/board.es?mid=a40305010000&bid=0019&act=view&list_no=138235&tag=&nPage=38, 2014. [Accessed 9 July 2020].
7. Wang S-I, Shen G-H, Shi H-C, Chiou S-J. Prescription patterns for tuberculosis treatment and adherence to treatment guidelines: a population-based study in Taiwan. *Pharmacoepidemiol Drug Saf* 2014;**23**:1273–80.
8. Xu L, Chen J, Innes AL, Li L, Chiang C-Y. Prescription practice of anti-tuberculosis drugs in Yunnan, China: a clinical audit. *PLoS One* 2017;**12**:e0187076.
9. Korean National Health Insurance Service (NHIS). *[15' NHIS] national health insurance system of Korea*. Available at: http://www.kobia.kr/bbs/board.php?tbl=policy_report&&category=&findEx=&findType=&findWord=&sort1=&sort2=&it_id=&shop_flag=&mobile_flag=&page=2. [Accessed 14 September 2020].
10. Lim S-S, Lee W, Kim Y-K, Kim J, Park JH, Park BR, et al. The cumulative incidence and trends of rare diseases in South Korea: a nationwide study of the administrative data from the National Health Insurance Service database from 2011-2015. *Orphanet J Rare Dis* 2019;**14**:49.
11. Chen YY, Pan SW, Shen HS, Chuang FY, Feng JY, Su WJ. Declining trend in incidence of tuberculosis in adolescents and young adults in Taiwan. *Eur Respir J* 2019;**53**:1801305.
12. Lee PH, Chan PC, Peng YT, Chu PW, Wu MH, Jou R. Impact of universal drug susceptibility testing and effective management of multidrug-resistant tuberculosis in Taiwan. *PLoS One* 2019;**14**(4):e0214792.
13. World Health Organization (WHO). *Global tuberculosis report*. Available at: https://www.who.int/tb/publications/global_report/en/, 2017. [Accessed 10 April 2021].
14. An J, Bai X, Gao M, Chu N, Huang H, Xu H, et al. Antituberculosis drug prescribing for inpatients in a national tuberculosis hospital in China, 2011–2015. *J Glob Antimicrob Resist* 2018;**14**:17–22.
15. Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, et al. Comparative roles of levofloxacin and ofloxacin in the treatment

of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. *Chest* 2003;**124**:1476—81.
16. Lee J, Lee CH, Kim DK, Yoon HI, Kim JY, Lee SM, et al. Retrospective comparison of levofloxacin and moxifloxacin on multidrug-resistant tuberculosis treatment outcomes. *Korean J Intern Med (Korean Ed)* 2011;**26**:153—9.
17. Kang YA, Shim TS, Koh WJ, Lee SH, Lee CH, Choi JC, et al. Choice between levofloxacin and moxifloxacin and multidrug-resistant tuberculosis treatment outcomes. *Ann Am Thorac Soc* 2016;**13**:364—70.
18. Caminero J. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tubercul Lung Dis* 2006;**10**:829—37.
19. World Health Organization (WHO). *Guidelines of the programmatic management of drug-resistant tuberculosis*. Available at: http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf, 2011. [Accessed 8 September 2020].
20. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. *Emerg update* 2008. Available at: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf. [Accessed 8 September 2020].
21. Kim S. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Eur Respir J* 2005;**25**:564—9.
22. Organization WH. *Anti-tuberculosis drug resistance in the world. Report No. 4: the WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance. Anti-tuberculosis drug resistance in the world Report No 4: the WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance*. 2008.
23. World Health Organization (WHO). *WHO consolidated guidelines on drug-resistant tuberculosis treatment*. Available at: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/, 2019. [Accessed 31 August 2020].
24. Korea Centers for Disease Control and Prevention (KCDC). *Korean guidelines for tuberculosis Fourth edition*. Available at: http://www.cdc.go.kr/board.es?mid=a20507020000&bid=0019&act=view&list_no=367154, 2020. [Accessed 31 August 2020].
25. Bestrashniy JRBM, Nguyen VN, Nguyen TL, Pham TL, Nguyen TA, Pham DC, et al. Recurrence of tuberculosis among patients following treatment completion in eight provinces of Vietnam: a nested case-control study. *Int J Infect Dis* 2018;**74**:31—7.
26. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. *J Clin Exp Hepatol* 2013;**3**:37—49.
27. World Health Organization (WHO) Europe. *Protocol 4. Management of tuberculosis and HIV coinfection. 2013 Revision*. Available at: https://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/publications/2013/2013-revision-protocol-4.-management-of-tuberculosis-and-hiv-co-infection. [Accessed 31 August 2020].
28. Milburn H, Ashman N, Davies P, Doffman S, Drobniewski F, Khoo S, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. *Thorax* 2010;**65**:557—70.