

Age-stratified anti-tuberculosis drug resistance profiles in South Korea: a multicenter retrospective study

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Abstract

Background: The emergence of drug-resistant tuberculosis (DR-TB) is a major healthcare concern worldwide. Here, we analyzed age-related trends in DR-TB rates in South Korea.

Methods: Drug susceptibility test results were collected from patients with culture-confirmed TB between 2015 and 2018 from eight university-affiliated hospitals. Patients were divided into three subgroups: younger (15–34 years), middle (35–59 years), and older (≥ 60 years) to compare drug-resistance patterns.

Results: Among the 4,417 cases investigated, 179 (4.1%), 53 (1.2%), and 316 (7.2%) were multidrug-resistant TB (MDR-TB), rifampicin-mono-resistant TB (RR-TB), and isoniazid-mono-resistant TB (Hr-TB), respectively. Proportions of Hr-TB cases were similar among the three groups (11.2%, 12.2%, and 10.4% in the younger, middle, and older groups, respectively). MDR/RR-TB case numbers decreased significantly as age increased (8.6%, 6.3%, 3.3%, respectively). Proportions of MDR/RR-TB among retreated patients in the younger generation decreased from 50.0% to 18.2%, but remained higher than that in the older generation. Fluoroquinolone resistance was highest among second-line drugs, and there were no differences in resistance to fluoroquinolones and second-line injectable drugs among the three age groups.

Conclusions: The number of MDR/RR-TB cases was highest in young patients. Effective public health interventions should include increased focus on rifampicin resistance in young patients.

Background

Drug-resistant tuberculosis (DR-TB) is a major global public health concern [1]. A 95% reduction in TB mortality and 90% reduction in its incidence compared to that in 2015 should be achieved by 2035 according to the World Health Organization (WHO)'s End TB strategy [2]. Preventing the spread of DR-TB is important for the elimination of TB [3]. Multidrug-resistant TB (MDR-TB), which is resistant to isoniazid (INH) and rifampicin (RIF), is another obstacle because of its high treatment costs and unsatisfactory outcomes.

Although anti-TB drug resistance rates declined after improved treatment efficiency in South Korea in the 1980s, nationwide drug surveillance conducted between 1994 and 2004 revealed that drug resistance had increased among new TB cases [4]. However, the nationwide trend of anti-TB drug resistance could not be estimated as this survey was discontinued and replaced with a new TB notification system [5]. The limited availability of data concerning drug resistance profiles thus hampers effective treatment of DR-TB.

The Korean War, which took place between 1950 and 1953, is regarded as the strongest causative factor for the TB epidemic in South Korea [6]. The period between 1965 and 1995 saw phenomenal economic growth and the expansion of national health insurance, leading to a dramatic decrease in TB incidence.

After 2000, incidence stagnated for a decade despite continuous national efforts to control the disease [7]. Considering South Korea's unique history of improved socioeconomic status and decreased TB incidence observed over a half century, we hypothesized that the degree and status of TB exposure in the younger generation differ from that in the previous generation, which may consequently affect drug resistance profiles. We therefore conducted a retrospective multicenter study to analyze drug resistance patterns associated with age among culture-confirmed TB cases.

Methods

Study design and data collection

We included native patients with phenotypic drug-susceptibility test (DST)-confirmed TB at eight university-affiliated hospitals in the Seoul metropolitan area and Daejeon between January 2015 and December 2018. Patients aged <15 years and foreign-born patients were excluded. We retrospectively reviewed medical records and collected age, gender, history of previous TB treatment, location of TB, and phenotypic DST data. Previous TB history was assessed by physicians via patient history-taking. If a patient had more than one DST result, only the earliest result was considered. If a patient had DST results for both pulmonary and extra-pulmonary specimens, results for the pulmonary specimen only were used.

Culture-based phenotypic drug susceptibility test

DST was performed in a supranational reference laboratory (Korean institute of Tuberculosis, Osong, South Korea) or other commercial reference laboratories. Workflows used and references of critical concentrations for resistance were the same in all reference laboratories. The drug susceptibility of *Mycobacterium tuberculosis* isolates was determined using an absolute concentration method with Lowenstein-Jensen medium, as recommended by the WHO.[8] Anti-TB drugs used and their critical concentrations for resistance were as follows: INH, 0.2 µg/mL; RIF, 40 µg/mL; ethambutol, 2.0 µg/mL; rifabutin, 20 µg/mL; streptomycin, 10 µg/mL; amikacin, 40 µg/mL; kanamycin, 40 µg/mL; capreomycin, 40 µg/mL; ofloxacin, 2.0 µg/mL; levofloxacin, 2.0 µg/mL; moxifloxacin, 2.0 µg/mL; prothionamide, 40 µg/mL; cycloserine, 30 µg/mL; para-aminosalicylic acid, 1.0 µg/mL. Pyrazinamide susceptibility was determined via pyrazinamidase test.

Definitions of variables

DR-TB cases were classified according to culture-based phenotypic DST results. DR-TB was defined as resistant to any anti-TB drug described, MDR-TB as resistant to both INH and RIF. RIF-mono-resistant TB (RR-TB) was defined as RIF-resistant but INH-susceptible, and INH-mono-resistant TB (Hr-TB) was defined as INH-resistant but RIF-susceptible. First-line drugs include INH, RIF, pyrazinamide, ethambutol, and streptomycin according to Korean TB guidelines [9]. New patients were defined as those never treated for TB or who had been prescribed anti-TB drugs for <1 month, according to the WHO's definition [10]. A patient with both pulmonary and extrapulmonary TB was classified as having pulmonary TB. We divided patients into three age groups based on socioeconomic background and TB status as follows: younger

generation, aged 15 to 34 years; middle generation, aged 35 to 59 years, and older generation, aged 60 years or older (Table 1).

Statistical analysis

Data are presented as numbers with percentages for categorical variables. To compare the differences between new and treatment cases, we performed both univariate and multivariate analyses using binary logistic regression. To evaluate trends in age-stratified DR, chi-squared tests for trend were performed. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows software (Statistical product and Service Solutions, ver. 15.0; IBM Co., Chicago, IL, USA).

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the Catholic Medical Center, the Catholic University of Korea approved the study protocol (XC19REDE0040) and waived the need for informed consent because no patients were at risk.

Results

After excluding 18 patients aged <15 years and 227 foreign-born patients, 4,417 native patients with TB, aged ≥ 15 years, were included in this analysis. Of those, 697 (15.7%) had a prior history of anti-TB treatment and 684 (15.5%) had DR-TB (Supplementary table 1). Advanced age, male gender, pulmonary involvement, and DR-TB infection were significantly associated with retreatment.

Among 4,417 patients enrolled, 316 (7.2%) had Hr-TB, 53 (1.2%) had RR-TB, and 179 (4.1%) had MDR-TB. The percentages of cases resistant to any fluoroquinolones (FQ) and any second-line injectable drugs (SLID) were 1.7% and 1.0%, respectively. The DR patterns of each age group are shown in Table 2. The percentage of Hr-TB cases among all patients enrolled was similar among the different age groups (11.2%, 12.2%, and 10.4% in the younger, middle, and older generation respectively). However, the percentage of Hr-TB in retreatment cases differed significantly among each age group and was highest in the older generation (5.9%, 5.5%, 11.3%, respectively; Supplementary Table 3). The number of MDR/RR-TB cases (resistant to RIF) was highest in the middle generation, and its proportion decreased significantly as age increased (8.6%, 6.3%, and 3.3%, respectively, $p = 0.000$). This pattern was observed in both new and retreated cases (Supplementary Tables 2 and 3). Among retreated cases, the percentage of cases resistant to any FQs (ofloxacin, levofloxacin, or moxifloxacin) and any SLIDs (amikacin, kanamycin, or capreomycin) was highest in the younger and middle generations, respectively.

INH and RIF resistance trends associated with age groups across each year are shown in Figures 1 and 2. The percentage of Hr-TB cases among new patients in the younger generation was lower than that in the older generation throughout the years. However, the opposite pattern was observed with regard to RR-/MDR-TB cases among new patients. The percentage of MDR/RR-TB cases among retreated patients

in the younger generation decreased from 50.0% in 2015 to 18.2% in 2018, but remained higher than that in the older generation.

We further analyzed patterns of resistance to FQs and SLIDs among Hr-TB, RR-TB, and MDR-TB cases. With the exception of first-line anti-TB drugs, resistance to FQs was the highest among that to second-line drugs (Table 3). The percentage of cases resistant to any FQs in Hr-TB, RR-TB, and MDR-TB cases was 1.3%, 1.9%, and 20.1%, respectively. In both non-MDR- and MDR-TB, the percentage of cases resistant to FQs did not differ significantly between age groups (Table 4). Of the 75 cases that were resistant to any FQs, 60 (80.0%) were resistant to ofloxacin, levofloxacin, and moxifloxacin (Supplementary Table 4). The percentage of cases resistant to any SLIDs in Hr-TB, RR-TB, and MDR-TB cases was 0.9%, 1.9%, and 14.5%, respectively (Table 3). In both non-MDR- and MDR-TB, the percentage of cases resistant to SLIDs did not differ significantly among age groups (Table 5). Of the 42 cases that were resistant to any SLIDs, 27 (64.3%) were resistant to both kanamycin and amikacin (Supplementary Table 5).

Discussion

This is the first study to compare percentages of DR-TB cases among various age groups in South Korea. The percentage of MDR/RR-TB cases was the highest in the younger generation, although that in retreated patients of the younger generation decreased between 2015 and 2018. The percentage of Hr-TB cases did not differ among the various age groups; however, it was higher among retreated patients in the older generation than that in the younger generation. Among the second-line anti-TB drugs, the percentage of cases resistant to any FQs was the highest and was similar among the various age groups. DR-TB is characterized by unfavorable outcome such as treatment failure, loss to follow-up and death, and leads to the spread of drug resistant organisms in the community as a result of inefficient interactions between the National Tuberculosis Control Program and patients with TB [4]. Therefore, understanding the prevalence and trends of drug resistance may help to identify TB treatment failures and determine the direction of future TB treatment policies.

MDR/RR-TB is a global public health concern and an important target for national TB control programs in many countries, including South Korea. According to a recent WHO report [11], an estimated 3.4% of new and 18% of previously treated TB cases were MDR/RR-TB. In South Korea, a recent study [5] revealed that the percentage of MDR/RR-TB among new and retreated cases between 2010 and 2014 decreased from 6.3–3.5% and from 29.4–19.2%, respectively. Similarly, in this study, 3.7% and 13.6% of new and retreated cases, respectively, were MDR/RR-TB. Although INH is an important drug which is safe and affordable, problems with Hr-TB have been neglected by the TB community [12]. The global percentage of Hr-TB cases is 7.2% of new and 11.6% of previously treated TB cases. In our study, the number of INH-resistant cases was higher than that of RIF-resistant cases among all TB patients, with 6.8% and 8.5% of new and retreated cases, respectively, being Hr-TB. The previous nationwide survey of anti-TB DR conducted in 2004 showed that the prevalence of Hr-TB among new and retreated cases was 5.1% and 6.8%, respectively, in South Korea [4]. Hr-TB and MDR/RR-TB cases should be continuously surveilled in order to assess their prevalence.

The great economic development and rapid decline of TB incidence observed during the last 50 years may have various impacts on drug resistance profiles in various age group. Korean patients born before 1950 likely experienced the explosion of the TB epidemic after the Korean War. During economic growth between the 1960s and 1970s, TB prevalence declined with the implementation of the national TB control program in 1960 [6]. In the 1960s and 1970s, triple therapy including INH and streptomycin was administered for 18 months. Indiscriminate use of anti-TB drugs and lack of patient management between the 1950s and 1970s may have led to the emergence of resistance to INH and streptomycin. Accordingly, our study revealed that among retreated cases, the percentage of Hr-TB cases in the older generation was the highest and almost twice that of the percentage in the younger and middle generations. This may be related to past exposure, including long-term and improper use of INH. Furthermore, INH resistance formed the highest percentage of all drug resistant cases in both new and retreated patients.

Since the 1980s, TB prevalence in South Korea decreased significantly compared to that in previous decades. In addition to having access to sustained economic development and universal health coverage, patients born after 1980 had a low chance of becoming infected with TB. A shorter regimen that included RIF and was administered for 6 to 9 months was also introduced in the 1980s. Our study showed that younger patients showed a higher percentage of RIF-resistant cases. This trend was consistent in both new and retreated patient groups, suggesting high rates of primary infection with MDR/RR-TB and acquired RIF resistance among young Korean patients. Although it is generally thought that a large percentage of MDR-TB cases arise from de novo resistance selection during previous TB treatment, the predominant incident MDR-TB etiology has now shifted to direct person-to-person MDR strain transmission [13]. A recent study suggested that > 80% of incident MDR-TB cases in most present-day epidemic settings result from transmission of MDR-TB [14]. Therefore, to control the MDR-TB epidemic in young patients, primary MDR-TB transmission and infection control and appropriate patient management should be prioritized in South Korea. In 2011, the Korean government implemented a national public-private TB control project, providing comprehensive TB patient management and treatment success rates among MDR-TB cases increased from 54.1% in 2014 to 64.3% in 2016 [7]. Furthermore, the percentage of MDR/RR-TB cases among young patients with prior TB history decreased dramatically between 2015 and 2016.

According to the revised WHO DR-TB treatment guidelines [15], levofloxacin is essential to MDR/RR- and Hr-TB treatment. FQs are widely used antimicrobial agents in out- and in-patient treatment, and its use in patients with TB at a single tertiary hospital in South Korea, regardless of their DR status, was also high [16]. Here, the percentage of FQ-resistant cases was the highest among that to second-line drugs, especially in young patients with prior anti-TB treatment history. In our study population, proportion of FQ resistance in both RR-TB and Hr-TB was low at 1.9% and 1.3%, respectively, which implies safe addition of levofloxacin to regimens according to the revised WHO guideline [15]. However, 26% of young patients with MDR-TB in our study population showed resistance to any FQs, implying a high public health burden in the younger generations. In addition, 25% of RIF- and INH-susceptible patients were resistant to any FQs, which is higher than results reported in a recent multi-country surveillance study [17]. Such a high

prevalence of FQ resistance may be due to the widespread use of FQs in various clinical settings [16]. Several studies showed that FQ exposure prior to TB diagnosis was associated with FQ resistance [18]. Therefore, the implementation of FQ prescription antibiotic stewardship programs for drug-susceptible TB should be considered in South Korea.

This study had several limitations. First, although we hypothesized that drug resistance profiles may differ among various age groups due to rapid and intense socioeconomic changes in late 20th century in South Korea, our cross-sectional study design could not confirm this. An age-period-cohort analysis is a better strategy to identify period and cohort effects on health [19]. The accumulation of repetitive cross-sectional data regarding drug resistance is necessary to perform such long-term analysis. Second, our results do not represent overall drug resistance in South Korea. However, because the eight participating university-affiliated hospitals are broadly located in several administrative districts and record approximately 2200 TB cases annually (almost 5% of all TB cases notified in South Korea), our study may reflect anti-TB drug resistance strains in South Korea. Third, the cause of high RIF resistance prevalence in the younger age group was not identified. Detailed data regarding prior anti-TB treatment and clinical information, which were not available here, are necessary to identify associated risk factors. Further epidemiological investigations including molecular and genomic typing may elucidate TB transmission routes and identify possible strategies.

Conclusions

We showed that anti-TB drug resistance profiles differ among patients in various age groups, with a high proportion of RIF and INH resistance in the young and elderly patient groups, respectively. Emerging FQ resistance, especially MDR/RR-TB, among young patients may limit anti-TB treatment strategies, and this should be regarded as a warning against the widespread use of FQ in the community [5]. In establishing future TB policies and treatment guidelines, differences in drug resistance patterns among age groups should be considered.

Abbreviations

DR-TB: Drug-resistant tuberculosis; DST: Drug-susceptibility test; FQ: fluoroquinolone; Hr-TB: INH-mono-resistant TB; INH: Isoniazid; MDR-TB: Multidrug-resistant TB; RIF: Rifampicin; RR-TB: RIF-mono-resistant TB; SLID: Second-line injectable drug; TB: Tuberculosis

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The Institutional Review Board of the Catholic Medical Center, the Catholic University of Korea approved the study protocol (XC19REDE0040) and waived the need for informed consent because no patients were at risk.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study design: JM, JSK. Data acquisition: JM, JYK, SKK, JWK, YHK, HKY, SHL, JSK. Data analysis: JM, HWK, JSK. Manuscript drafting: EGL, JM, JSK. Critical manuscript revision: EGL, JM, HYK, JSK. All authors read and approved the final manuscript.

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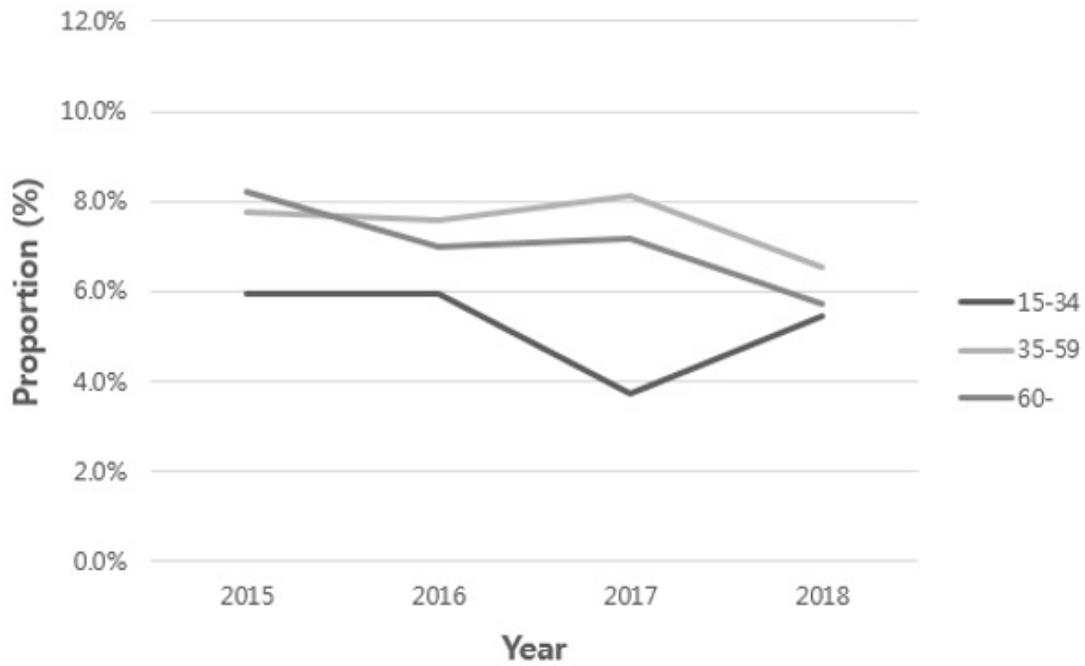
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Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures

A



B

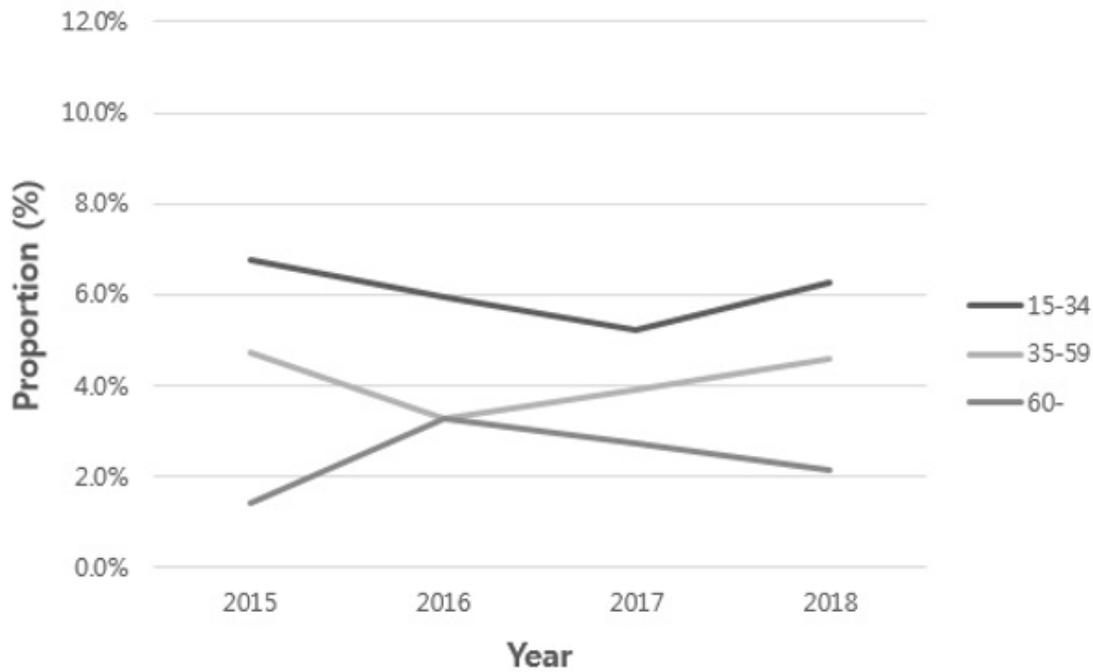


Figure 1

Trend of drug-resistant profiles among new patients stratified by the age groups in each calendar year. A) Proportions of Hr-TB, B) Proportions of MDR/RR-TB. Hr-TB = isoniazid-mono-resistant tuberculosis; MDR/RR-TB = multidrug-resistant/rifampicin-mono-resistant tuberculosis.

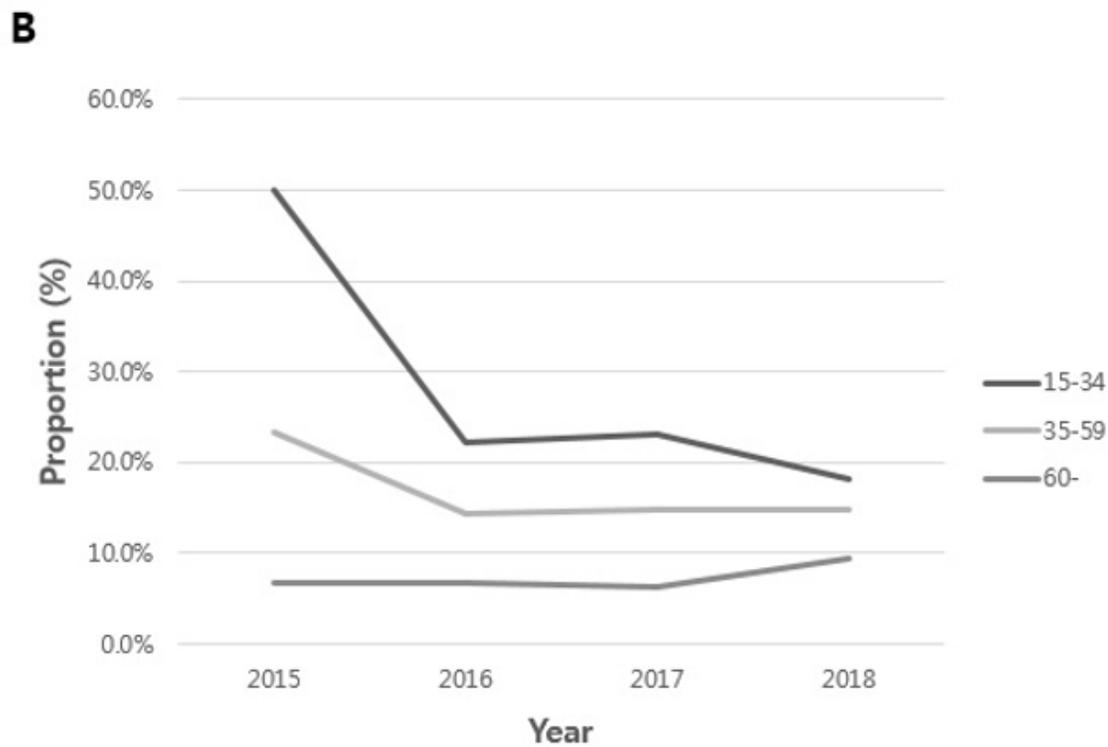
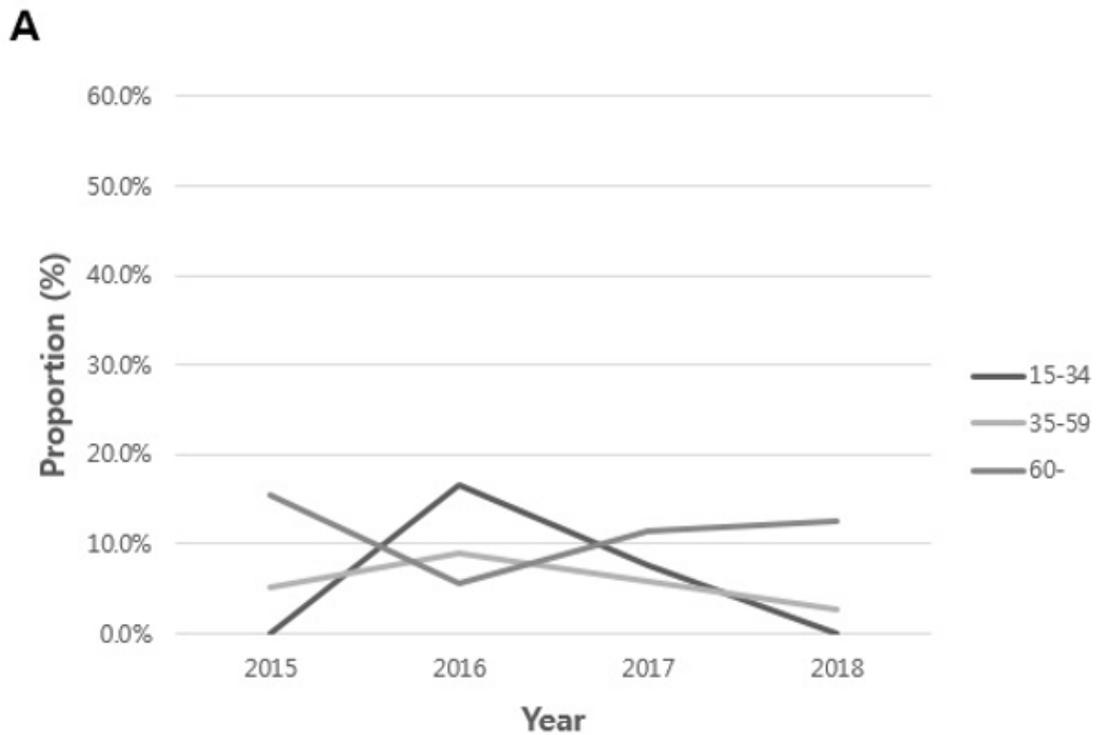


Figure 2

Trend of drug-resistant profiles among retreatment patients stratified by the age groups in each calendar year. A) Proportions of Hr-TB, B) Proportions of MDR/RR-TB. Hr-TB = isoniazid-mono-resistant tuberculosis; MDR/RR-TB = multidrug-resistant/rifampicin-mono-resistant tuberculosis.

Supplementary Files

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