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Original Article

Surveillance of multidrug-resistant tuberculosis in Taiwan, 2008–2019

Mei-Hua Wu [a,b], Hseuh-Chien Hsiao [a,b], Po-Wei Chu [c], Hsin-Hua Chan [a,b], Hsiu-Yun Lo [c], Ruwen Jou [a,b,d,*]

[a] *Tuberculosis Research Center, Taiwan Centers for Disease Control, Ministry of Health and Welfare Taipei, Taiwan*
[b] *Reference Laboratory of Mycobacteriology, Taiwan Centers for Disease Control, Ministry of Health and Welfare, Taipei, Taiwan*
[c] *Chronic Infectious Disease Division, Taiwan Centers for Disease Control, Ministry of Health and Welfare, Taipei, Taiwan*
[d] *Institute of Microbiology and Immunology, National Yang Ming Chiao Tung University, Taipei, Taiwan*

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KEYWORDS
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Abstract *Background:* Drug-resistant tuberculosis (DR-TB) is a major contributor to global cases of antimicrobial resistance and remains a public health challenge. To understand the extent and trend of DR-TB under an enhanced multidrug-resistant TB (MDR-TB) management program, we conducted a population-based retrospective study of 1511 Taiwanese MDR-TB cases reported from 2008 to 2019.
Methods: We obtained patient demographics and clinical and bacteriological information from the National TB Registry and the Infectious Disease Notification System.
Results: Of the 1511 MDR-TB patients, 941 were new cases, 485 were previously treated, and 85 had an unknown history of treatment. The male to female ratio was 2.75, and the median age of the patients was 57 years (IQR: 45–72). We observed a significant decline in MDR-TB cases, with annual percentage change (APC) of −4.17%. However, new and previously treated MDR-TB cases had APCs of −1.41% and −9.18%, respectively. The rates of MDR-TB resistance to ethambutol, streptomycin and pyrazinamide were 47.2%, 42.4% and 28.9%, respectively, whereas the rates of resistance to fluoroquinolones and second-line injectable drugs (SLIDs) were 4.1–7.1%, 9.0–14.1%; and the rate of extensively drug-resistant TB was 1.9%, respectively. Furthermore, we observed a decreasing trend of resistance to SLIDs (APCs −7.0% to −8.2%) in new cases and a significant decreasing trend of resistance to moxifloxacin (−24.6%) and levofloxacin (−23.3%) in previously treated cases.

* Corresponding author. Tuberculosis Research Center, Taiwan Centers for Disease Control, Ministry of Health and Welfare Taipei, Taiwan. Fax: +8862 2653-1387.
E-mail addresses: rwj@cdc.gov.tw, rwj2007@gmail.com (R. Jou).

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Conclusion: The decreasing trend of MDR-TB and resistance to second-line drugs suggested that our programmatic management of TB was effective and that the impact on TB control was profound.

Introduction

The World Health Assembly called on all nations and the international community to take actions to control antimicrobial resistance, including surveillance, in 2014.[1] Drug-resistant tuberculosis (TB) is a major contributor to global cases of antimicrobial resistance and remains a public health challenge. As early as 1994, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance to measure the magnitude and monitor trends of drug resistance was established by the Global Tuberculosis Program of the World Health Organization (WHO), with the support of the International Union against Tuberculosis and Lung Disease (UNION) and the TB Supranational Reference Laboratory (SRL) Network.[2]

External quality assurance (EQA), such as proficiency testing of drug susceptibility testing (DST) for *Mycobacterium tuberculosis*, has been conducted for first-line drugs by the SRL network since 1994.[3] Quality-assured data are collected either through continuous surveillance systems based on routine testing of all TB patients or periodic surveys of representative populations. The WHO published the first global report on drug-resistant TB in 1997 and 5 global reports by 2010.[4] Subsequently, drug-resistance surveillance data have been published annually in the WHO Global TB Report.[5]

TB is a major notifiable infectious disease in Taiwan. In 2019, the incidence rates of new TB and MDR-TB cases were 8732 (37 per 100,000 population) and 79, respectively. Since 2003, the NRL has been participating in the SRL external quality assessment of TB DST, and the laboratory-based Taiwan Surveillance of Drug-Resistant TB was established.[6] We reported results of combined anti-tuberculosis drug resistance from surveys conducted in 2004—2005.[6] Hospital-based studies revealed significant decreasing trends of first-line drug resistance in Northern Taiwan from 2000 to 2006 ($P < 0.001$) and Central Taiwan from 2003 to 2007 ($P < 0.05$).[7,8]

Since 2007, the Taiwan CDC, the National Reference Laboratory (NRL) of Mycobacteriology at the Taiwan Centers for Disease Control (TCDC), has conducted annual first-line anti-TB drug proficiency testing and rechecking of RR/MDR *M. tuberculosis* for all clinical TB laboratories performing DST in Taiwan. The results have been satisfactory. Currently, the TB laboratory network in Taiwan achieves universal DST, with 98.5% of culture-positive pulmonary TB cases having results under an EQA program. Another report on population-based drug-resistance surveillance of MDR-TB revealed a significant decreasing trend in new cases of MDR-TB ($P < 0.0001$) and a decreasing trend of resistance to pyrazinamide (PZA), ofloxacin (OFX) and p-aminosalicylic acid (PAS) from 2007 to 2014.[9]

In the Taiwan TB control program, an MDR-TB case must be bacteriologically confirmed, and drug susceptibility to PZA and second-line drugs is assessed by the NRL. Our drug-resistance survey is based on a population-based continuous surveillance system. This is an in-depth report describing the burden and trends of anti-TB drug resistance among MDR-TB cases reported from 2008 to 2019.

Methods

Study design

This was a population-based retrospective study of MDR-TB cases reported from 2008 to 2019. The MDR-TB were categorized based on demographic and clinical information entered into the National TB Registry. A new case was defined as one that had never been reported or recorded in the TB Registry as an MDR-TB case. Previously treated MDR-TB cases included recurrent cases, treatment after loss to follow-up cases, treatment after failure cases and other previously treated cases. We retrieved patient demographics, clinical information, acid-fast bacilli (AFB) smear results and chest radiological findings from the National TB Registry. Routine AFB smear microscopy, mycobacterial culture, and subsequent identification and drug susceptibility testing (DST) were performed. The results of conventional bacteriological tests were obtained from either paper reports or the National TB Registry before 2013; automatically uploaded to the Infectious Disease Notification System through the Infectious Disease Reporting System from 2013 to October 2019; and through the National Laboratory Information Management System (LIMS) from November 2019. MDR MTBC isolates were sent to the reference laboratory of the Taiwan CDC for confirmation using genotypic and phenotypic DST for isolates with discordant results. In addition, data of TB other than MDR-TB were obtained directly from annual Taiwan Tuberculosis Control Report for analyses. General smear-positive TB is defined as any bacteriologically confirmed primary-TB case with a positive AFB-smear result; whereas, general pulmonary-TB is defined as any bacteriologically confirmed or clinically diagnosed TB case involving the lung parenchyma or the tracheobronchial tree. A patient with both pulmonary and extrapulmonary TB is classified as a pulmonary case.

AFB smear microscopy

Concentrated sputum smears were prepared using the NALC-NaOH method. Microscopy with the centrifuged

sediments of the concentrated samples was performed using auramine O fluorescent staining, and a positive smear was further confirmed using Ziehl-Neelsen staining. The AFB smear results were interpreted according to the guidelines issued by the American Thoracic Society.[10]

Mycobacterial culture, identification and drug susceptibility testing

Decontaminated specimens were inoculated on solid and into liquid media. The MPB64 antigen of MTBC was detected as previously described. MDR *M. tuberculosis* isolates were subjected to DST using the agar proportion method (APM) with 7H10 and 7H11 media (Coning Technology Limited Company, Taiwan). Drug resistance was defined as the growth of 1% of colonies in a drug-containing medium. According to WHO recommendations, the critical concentrations of the tested drugs in 7H10 media were RIF, 1 mg/L; INH, 0.2 mg/L; ethambutol (EMB), 5 mg/L; streptomycin (STM), 2 mg/L; OFX, 2.0 mg/L; levofloxacin (LFX), 1 mg/L; and moxifloxacin (MXF), 0.5 mg/L. The critical concentrations of the tested drugs in 7H11 media were rifabutin (RFB), 0.5 mg/L; AMK), 6 mg/L; KAN, 6 mg/L; CAP, 10 mg/L; ethionamide (ETO), 10 mg/L; PAS, 8.0 mg/L and D-cycloserine (DCS), 60 mg/L. Resistance to PZA, 100 mg/L, was tested using the Bactec MGIT 960 system (Becton Dickinson Diagnostic Systems, Sparks, MD) as described previously. Growth on a control medium was compared to growth on the corresponding drug-containing medium to determine susceptibility. The DST result was used to determine resistance or susceptibility. The tests were validated based on the susceptibility of *M. tuberculosis* H37Rv. Since STM was initially tested with RIF, INH and EMB as first-line drugs, we categorized STM as a first-line drug. MDR is defined as an *M. tuberculosis* isolate that is resistant to at least INH and RIF. Pre-XDR is defined as an MDR isolate that is resistant to either fluoroquinolones (FQs) (pre-XDR fluo) or at least one of the injectable drugs (pre-XDR inj). XDR was defined as MDR TB plus resistance to an FQ and at least one SLID.

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as counts and proportions and were compared using the chi-square test. Continuous variables with normal distribution were described by the mean and standard deviation (SD) and were compared using Student's *t* test for two independent samples. Differences in drug resistance between age groups, sexes, ethnicity, AFB smear, Chest radiography, pleural effusion and site of TB were analyzed using the χ^2 test or Fisher's exact test. Statistical significance was achieved at a significance level of 0.05. Joinpoint version 4.9.0.0. was used to analyze the trend of rates, timepoint of changes and significance of resistance to first- and second-line drugs from 2008 to 2019.[11,12] Since incidence rates change at a constant percentage every year and change linearly on a log scale, the annual percentage change (APC) was obtained using the results of natural logarithm calculations.[11,13]

Results

Characteristics of the study population

From 2008 to 2019, 1625 MDR-TB cases were registered, of which 32 cases had no data including 4 cases with culture contaminated, 11 cases recategorized due to discordant genotypic and phenotypic DST results and 17 confirmed cases with missing bacteriological data. Excluding 82 non-Taiwanese cases and the above-mentioned 32 cases, we included 1511 (93%) MDR-TB cases in this study (Table 1). The ratio of male to female MDR-TB patients was 2.75, which was higher than that of the general TB population (2.2).[14] The ratio of males to females in previously treated cases and new cases was 3.04 and 2.76, respectively ($P = 0.456$). Overall, a higher percentage of males to females was found in the general TB and MDR-TB cases.

The mean age of the MDR-TB patients was 57.5 years old (range: 13—100 years) and that of the new patients and previously treated patients was 57.5 years old (range: 13—98 years) and 56.5 years old (range: 16—100 years), respectively. The majority of the MDR-TB patients were in the ≥65 (35.6%) and 55—64 (21.8%) years old age groups (Table 1). Compared with the previously treated patients, we found a significant increase in the number of new patients in the 0- to 24-year-old age group ($P < 0.05$).

The AFB-smear positive rate was 54.7%, which was higher than that of all TB cases (38%) ($P = 0.133$).[14] In addition, 1375 (91.0%) MDR-TB patients had pulmonary TB, which was higher than that of global general TB population (84%).[15]

Time trend of tuberculosis and MDR-TB cases

Of the 1511 MDR-TB patients, there were more new patients (941 (62.3%)) than previously treated patients (485 (32.1%)) (Fig. 1). Furthermore, the majority of the previously treated cases were relapse (61%) and treatment after failure (30.5%) (Fig. 1). The incidence of new TB cases was 62 in 2008, which declined to 37 per 100,000 population in 2019 ($P < 0.01$, Fig. 2). The annual number of MDR-TB cases gradually decreased from 156 to 73 from 2008 to 2019 (Fig. 2). We observed decreasing trends of new TB and previously treated MDR-TB cases with APCs of −4.46% ($P < 0.001$) and −9.18% ($P < 0.001$), respectively (Fig. 2). Whereas, the APC of new MDR-TB cases was −1.41% ($P = 0.3$).

Surveillance of drug resistance

Of the 1511 MDR-TB cases, we identified 247 (16.4%) pre-XDR and 29 (1.9%) XDR-TB cases (Table 2). For first-line drug resistance, the resistance ratios were 47.2% and 28.9% to EMB and PZA, respectively. Furthermore, EMB resistance was higher in new cases (50.4%), and PZA resistance was higher in previously treated cases (33.0%). Compared with new MDR-TB cases, the P-value of EMB resistance for relapse, treatment after failure and lost to follow-up MDR-TB cases was 0.130, 0.017 and 0.648, respectively; whereas, that of PZA resistance was 0.051, 0.099 and 0.462, respectively. For FQ resistance, the resistance ratios were 10.6% and 9.0% to MFX and LFX, respectively. Notably, new

Table 1 Demographics and clinical characteristics of 1511 MDR-TB cases in Taiwan, 2008—2019.

Characteristic	The number of total cases (N, %)	The number of new cases (N, %)	The number of previously treated cases (N, %)	The number of unknown treatment history cases (N, %)	P value
Sex					0.456
Male	1108 (73.3)	691 (73.4)	365 (75.3)	52 (61.2)	
Female	403 (26.7)	250 (26.6)	120 (24.7)	33 (38.8)	
Age group, years					0.065
5—14	2 (0.1)	1 (0.1)	0 (0.0)	1 (1.2)	
15—24	65 (4.3)	49 (5.2)	14 (2.9)	2 (2.4)	
25—34	117 (7.7)	74 (7.9)	37 (7.6)	6 (7.1)	
35—44	183 (12.1)	104 (11.1)	71 (14.6)	8 (9.4)	
45—54	277 (18.3)	172 (18.3)	92 (19.0)	13 (15.3)	
55—64	329 (21.8)	201 (21.4)	119 (24.5)	9 (10.6)	
>65	538 (35.6)	340 (36.1)	152 (31.3)	46 (54.1)	
Ethnicity					0.040
Nonindigenous	1309 (86.6)	837 (88.9)	404 (83.3)	68 (80.0)	
Indigenous	168 (11.1)	98 (10.4)	67 (13.8)	3 (3.5)	
Unknown	34 (2.3)	6 (0.6)	14 (2.9)	14 (16.5)	
AFB smear					0.133
Negative	637 (42.2)	415 (44.1)	190 (39.2)	32 (37.6)	
Positive	826 (54.7)	511 (54.3)	278 (57.3)	37 (43.5)	
Unknown	48 (3.2)	15 (1.6)	17 (3.5)	16 (18.8)	
Chest radiography					0.071
Normal	24 (1.6)	13 (1.4)	8 (1.6)	3 (3.5)	
Abnormal with cavitation	388 (25.7)	232 (24.7)	145 (29.9)	11 (12.9)	
Abnormal without cavitation	1037 (68.6)	675 (71.7)	306 (63.1)	56 (65.9)	
Abnormal but not related to TB	23 (1.5)	14 (1.5)	9 (1.9)	0	
Unknown	39 (2.6)	7 (0.7)	17 (3.5)	15 (17.6)	
Pleural effusion					<0.001
No	1421 (94.0)	871 (92.6)	473 (97.5)	77 (90.6)	
Yes	90 (6.0)	70 (7.4)	12 (2.5)	8 (9.4)	
Site of TB					0.015
Pulmonary	1375 (91.0)	842 (89.5)	453 (93.4)	80 (94.1)	
Extrapulmonary	136 (9.0)	99 (10.5)	32 (6.6)	5 (5.9)	
Pleural TB	52 (38.2)	45 (45.5)	7 (21.9)	0	
Other organ TB	28 (20.6)	19 (19.2)	7 (21.9)	2 (40)	
Lymph node TB	17 (12.5)	11 (11.1)	5 (15.6)	1 (20)	
Skeletal TB	12 (8.8)	7 (7.1)	5 (15.6)	0	
Gastrointestinal TB	9 (6.6)	6 (6.1)	3 (9.4)	0	
Urogenital TB	6 (4.4)	4 (4.0)	1 (3.1)	1 (20)	
Cutaneous and ocular TB	6 (4.4)	4 (4.0)	2 (6.3)	0	
TB meningitis	5 (3.7)	2 (2.0)	2 (6.3)	1 (20)	
Nasopharynx TB	1 (0.7)	1 (1.0)	0 (0.0)	0	

cases had higher resistance ratios for MFX (11.1%) and LFX (9.2%). The resistance ratios for SLIDs resistance were between those for KAM (7.1%) and CAP (4.1%). Higher ratios of SLIDs resistance were found in previously treated cases. In addition, the RBT cross-resistance ratio was 86.3% and 81.6% in new and previously treated cases, respectively (Table 2).

Time-trend analysis of drug resistance

The time trend and APCs of resistance to first-line drugs and second-line drugs in the MDR-TB cases are shown in Fig. 3. Among the first-line drugs, trends of resistance to EMB, PZA and STM steadily increased over the years without statistical significance. In new cases, the trends were +1.2, +0.7 and +0.2 per annum, respectively. In the previously treated cases, the trends were +3.0, +0.6, and +1.5 per annum, respectively. For the SLIDs, we observed decreasing trends of resistance to KAN in both new (−8.2 per annum) and previously treated (−2.6 per annum) cases. However, we found decreasing trends of resistance to AMK (−7.0 per annum) and CAP (−7.9 per annum) in new cases and increasing trends of resistance to AMK (+3.3 per annum) and CAP (+5.3 per annum) in previously treated cases. For

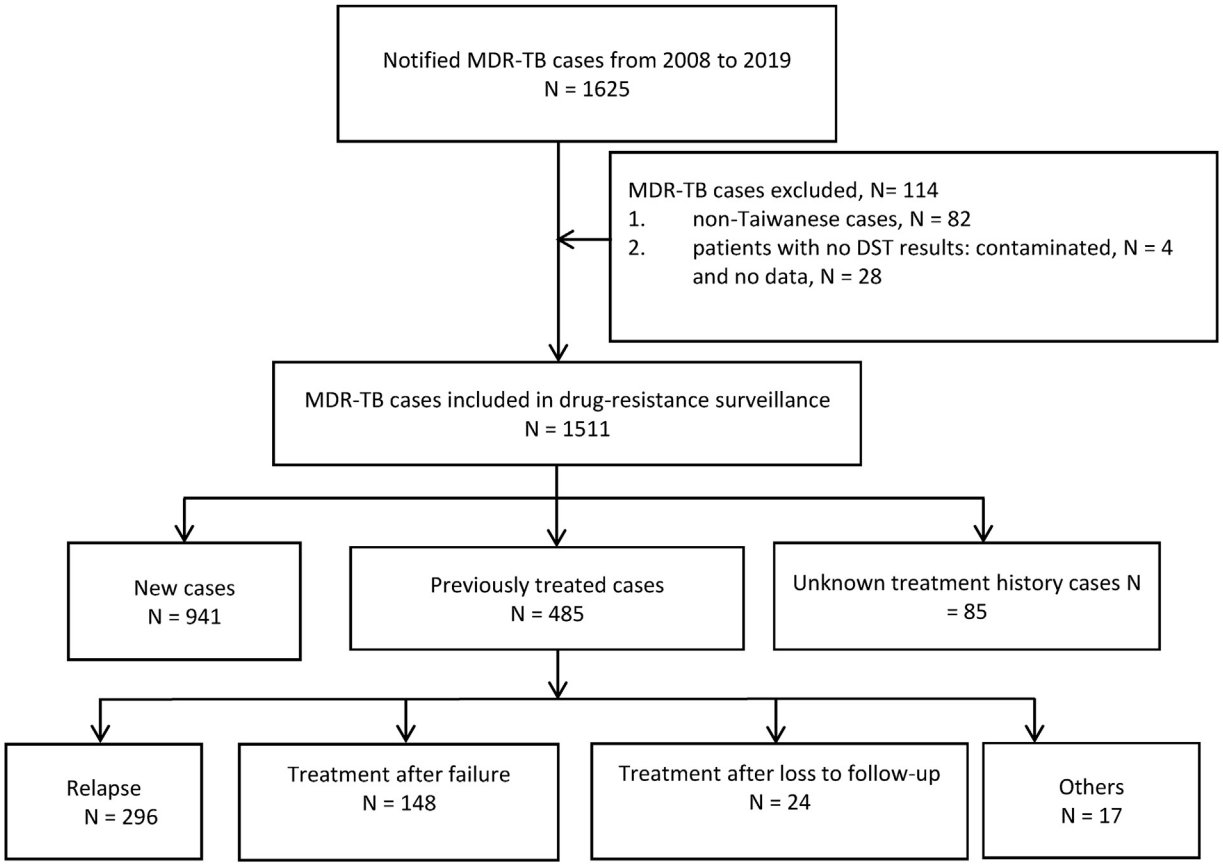

Figure 1. Flow diagram of the study population. MDR, multidrug-resistant tuberculosis; DST, drug susceptibility testing.

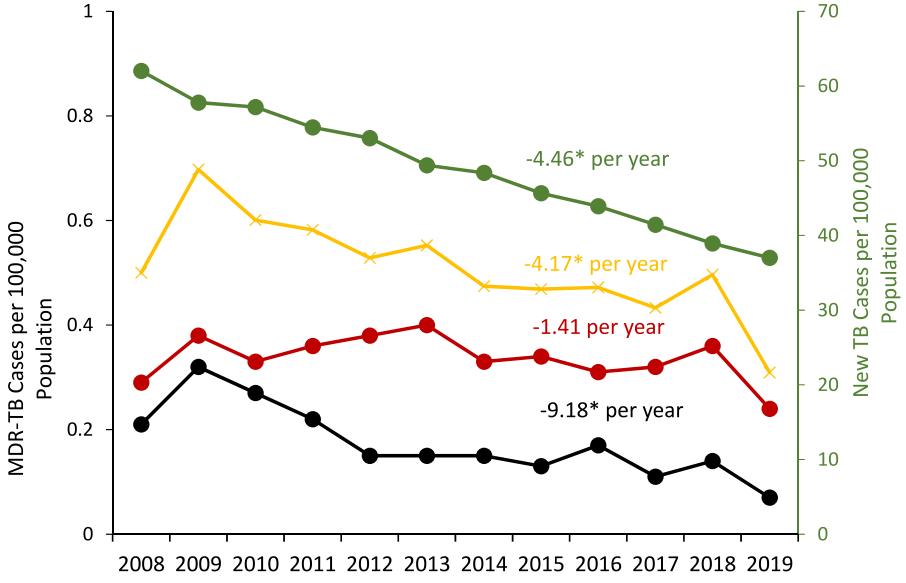

Figure 2. Time trend of newly diagnosed tuberculosis (green circles), multidrug-resistant TB (MDR-TB) (yellow cross) and previously treated MDR-TB cases (black circles) with significant decreasing trends and new MDR-TB (red circles) cases with a decreasing trend from 2008 to 2019. The mean change per year is given as a percentage.

other second-line drugs, we observed an increasing trend of resistance to RBT (+0.4 per annum) in previously treated cases and a decreasing trend of resistance to ETH (−0.7 and −4.4 per annum) in new and previously treated cases, respectively. A decreasing trend of resistance to PAS (−3.6 per annum) was found in new cases, and the trend of changes showed a significant decline (−24.6 per annum) from 2008 to 2012 and an upward trend (11.97 per annum)

Table 2 Drug-resistance patterns of 1511 MDR-TB cases in Taiwan, 2008—2019.

Drug susceptibility (No of isolates tested)	The number of total cases,No (%)	The number of new cases,No (%)	The number of previously treated cases, No (%)	The number of treatment history unknown cases, No (%)	P value
Any resistance to streptomycin and first-line drugs					
Ethambutol (1460)	689 (47.2)	462 (50.4)	202 (43.9)	25 (30.1)	0.023
Pyrazinamide (1510)	436 (28.9)	250 (26.6)	160 (33.0)	26 (30.6)	0.012
Streptomycin (1457)	618 (42.4)	405 (44.3)	177 (38.6)	36 (43.4)	0.044
Any resistance to fluoroquinolones[a]					
Ofloxacin (1140)	161 (14.1)	87 (12.9)	55 (14.4)	19 (22.4)	0.485
Moxifloxacin (802)	85 (10.6)	64 (11.1)	20 (8.9)	1 (100)	0.370
Levofloxacin (829)	75 (9.0)	55 (9.2)	19 (8.2)	1 (100)	0.621
Any resistance to second-line injectable drugs					
Kanamycin (1511)	108 (7.1)	56 (6.0)	41 (8.5)	11 (12.9)	0.076
Amikacin (1511)	72 (4.8)	39 (4.1)	28 (5.8)	5 (5.9)	0.081
Capreomycin (1511)	62 (4.1)	34 (3.6)	23 (4.7)	5 (5.9)	0.159
Any resistance to other second-line agents					
Rifabutin (1509)	1284 (85.1)	812 (86.3)	394 (81.6)	78 (91.8)	0.019
Ethionamide (1509)	454 (30.1)	281 (29.9)	149 (30.8)	24 (28.2)	0.701
Para-aminosalicylic acid (1510)	114 (7.5)	56 (6.0)	45 (9.3)	13 (15.3)	0.020
Cycloserine (1398)	7 (0.5)	5 (0.6)	2 (0.4)	0	0.789
Drug-resistance pattern[b]					
Simple MDR (1511)	1235 (81.7)	784 (83.3)	393 (81.0)	58 (68.2)	0.169
Pre-XDR fluo (1511)	161 (10.7)	98 (10.4)	47 (9.7)	16 (18.8)	
Pre-XDR inj (1511)	86 (5.7)	46 (4.9)	32 (6.6)	8 (9.4)	
XDR-TB (1511)	29 (1.9)	13 (1.4)	13 (2.7)	3 (3.5)	

[a] Ofloxacin tested during 2008—2015; moxifloxacin and levofloxacin tested during 2013—2018.
[b] MDR-TB, multidrug-resistant tuberculosis; Pre-XDR fluo, pre-extensively drug-resistant tuberculosis with any fluoroquinolone resistance; Pre-XDR inj, pre-extensively drug-resistant tuberculosis with any injectable-drug resistance; XDR-TB, extensively drug-resistant tuberculosis.

from 2012 to 2019 in previously treated cases. For FQs, we observed a decreasing trend of OFX resistance in both new (−0.77 per annum) and previously treated (−4.34 per annum) cases; for LFX resistance, we found an increasing trend in new cases (+7.8 per annum) and a decreasing trend in previously treated cases (−23.3 per annum), whereas there were decreasing trends of resistance to MFX in both new (−0.54 per annum) and previously treated (−24.6 per annum) cases. Notably, significant decreasing trends were observed in resistance to MFX and LFX in previously treated cases, and an increasing trend in resistance to PAS was observed in new cases from 2012 to 2019.

Discussion

This population-based survey conducted from 2008 to 2019 in Taiwan reports the trends and prevalence of MDR-TB. Universal DST for TB and timely web-based reporting have been implemented in Taiwan. The DST data in the registration database of the Taiwan CDC were obtained from accredited TB laboratories under an EQA program.[16] In Taiwan, *M. tuberculosis* resistance to INH was 8% and 17% in new and previously treated TB cases, respectively, and resistance to RIF was 1% and 8% in 2019.[17] Furthermore, the MDR ratios were 1% and 8% in new and previously treated TB cases, respectively. The WHO estimated that 0.5 million global TB cases were MDR-TB in 2019, and 3.3% and 17.7% were found in new and previously treated TB cases, respectively.[15] However, the estimated proportions of new cases and previously treated cases of MDR/RR-TB were 4.6% and 24%, respectively, in the WHO western Pacific region where Taiwan is located.[15] From 2008 to 2019, we observed a decreasing trend in new TB (APC = −4.46%) cases, which was better than that of global TB (APC = −2%). In addition, a −4.17% annual decrease rate in MDR-TB cases over the years in Taiwan was better than the global average decrease rate of −1.95%.[13]

The 2020 Global TB Report revealed sex inequality in TB incidence, with a male to female ratio of 1.6:1 globally and 2.0:1 in the WHO Western Pacific region.[15] The sex differences among patients with TB are crucial for instituting effective prevention and treatment. In this survey, we observed marked differences in TB, MDR-TB and XDR-TB epidemiology for men and women, with a ratio of 2.74—3.1. Smoking, occupational exposures and other sociocultural conditions may put men at higher risks of TB. Based on the National TB Registry, 51.5—60% of all annual TB patients were over 65 years old, with a significant decreasing trend of age-specific incidence from 314 in 2008 to 143.7 per 10,0000 population in 2019 ($P < 0.001$). The WHO reported that there was an age-dependent decrease in MDR-TB in most countries.[18] We have observed a significant decreasing trend of MDR-TB cases with an APC of −4.17% from 2008 to 2019. Nevertheless, we observed increasing trends of MDR-TB cases with increasing age in both new and previously treated patients (Table 1).

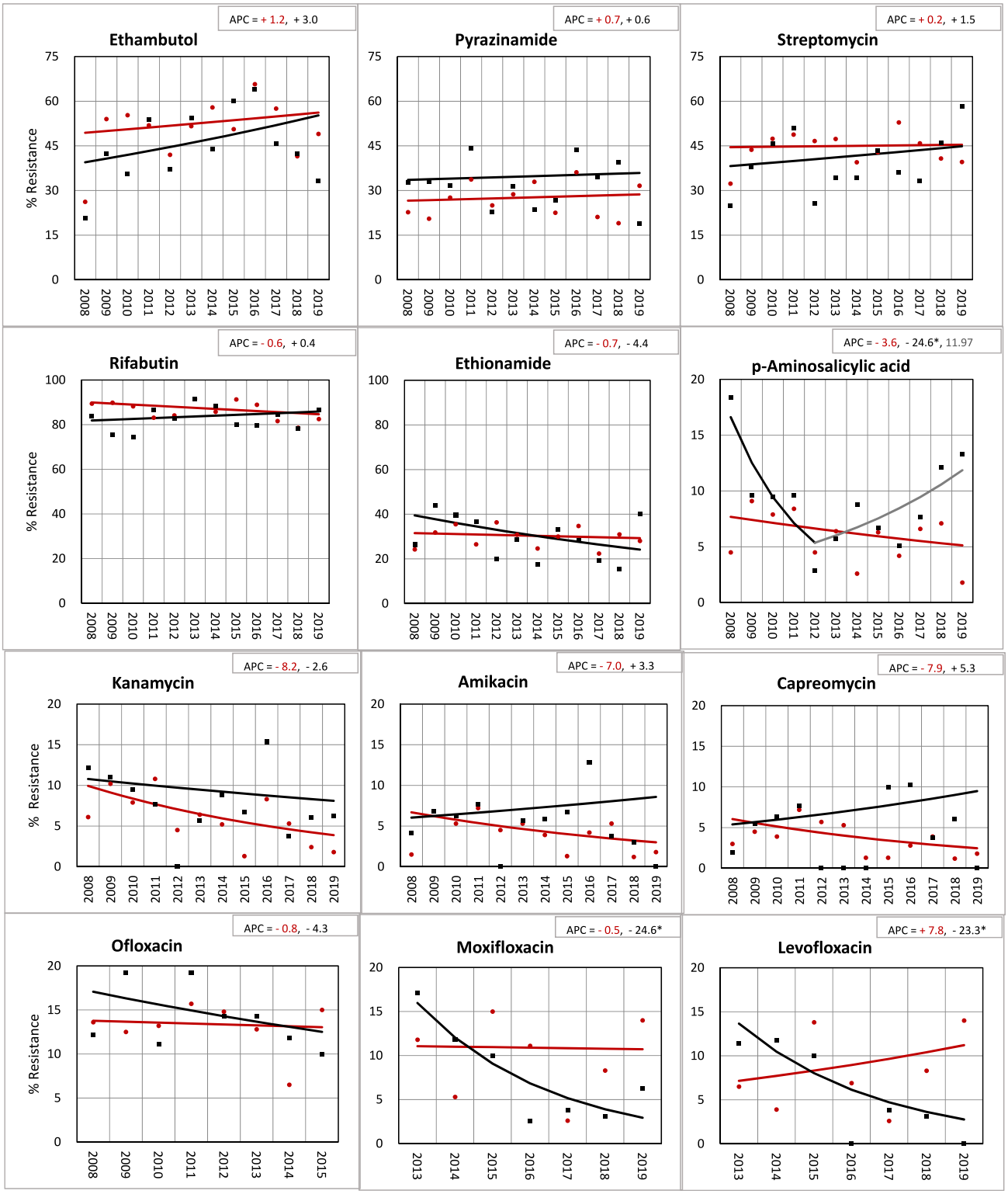

Figure 3. Time trends of the resistance rate to first-line and second-line drugs in new MDR-TB cases (red circles) and previously treated MDR-TB cases (black squares). The mean change per year is given as a percentage. —: APC of new MDR-TB; —: APC of previously treated MDR-TB; *: $P < 0.05$.

Furthermore, this survey revealed that 35.6% of MDR-TB patients were over 65 years old, and an increasing trend was observed from 25.4% in 2008 to 49.3% in 2019 ($P < 0.001$) (Supplementary Table). The impact of the aging population on MDR-TB epidemics merits further investigation. Furthermore, the AFB-smear positive rate was 54.7%, which is higher than that of general TB cases. Therefore, control measures such as early diagnosis, prompt

treatment, and proper contact tracing along with preventive therapy for latent-infected cases are suggested.[19]

Significant declining trends of TB (APC = −4.46%) and all MDR-TB (APC = −4.17%) cases might be the result of implementing diagnosis policies to adapt and expand molecular diagnoses for all AFB smear-positive presumptive cases and MDR-TB high-risk populations, respectively (Table 2). Nevertheless, the slow decline in new MDR-TB cases (APC = −1.41%) indicated unidentified sources of infection. To reinforce our MDR-TB control program, contact tracing based on the results of whole-genome sequencing was implemented. Notably, a significant decrease in previously treated cases (APC = −9.18%) indicating directly observed therapy, short course (DOTS) for TB cases and DOTS-Plus for cases of drug-resistant TB in Taiwan (DOTS) were effective.[20] In Taiwan, MDR-TB policies for rapid molecular testing, reporting and management, strengthening contact tracing and restricting FLQ prescriptions have been enforced stepwise since 2007.[21] In addition, to strengthen the programmatic management of drug-resistant TB (PMDT), the Taiwan MDR-TB Treatment Consortium (TMTC) was established in 2007; 82.4% of the MDR-TB patients cared in the consortium had 82.9% favorable treatment outcomes. The effective PMDT had a significant impact on the epidemic of MDR-TB.[21]

In this survey, the trend of EMB and PZA resistance was APC = +1.2% and APC = +0.7% in MDR-TB cases, respectively. We observed that the prevalence of EMB and PZA resistance is not significantly higher in previously treated MDR-TB cases than new MDR-TB cases, except EMB-resistant MDR-TB cases was significantly higher among treatment after failure cases. Since approximately 70% of MDR-TB was new cases in Taiwan, transmission of MDR *M. tuberculosis* with concurrent EMB/PZA resistance might contribute to higher resistance ratios in new cases. Studies revealed that PZA resistance in *M. tuberculosis* arises after RIF and fluoroquinolone (FQ) resistance and is likely to have concomitant resistance to STM, EMB, OFX, LFX and pre-XDR.[22,23] Even though we observed relatively high FQ resistance in new MDR-TB cases, the associations with higher EMB and PZA resistance found in new MDR-TB need further investigations.

EMB and PZA are often used in combination with various second-line drugs to treat DR-TB. A 2018 WHO guideline categorized EMB and PZA as Group C drugs for MDR/XDR-TB treatment. In addition, the WHO published consolidated guidelines on INH-resistant TB in 2019; the key recommendations are treatment with RIF-EMB-PZA-LFX for 6 months without injectable agents. In our MDR-TB cohort, resistance to EMB was 47.2%, which is comparable to that in China, where 56.8% of MDR-TB isolates were resistant to EMB, and in Europe (59.3%).[24,25]

Globally, the estimated pooled PZA resistance in all TB and MDR-TB cases was 16.2% (95% CI 11.2—21.2) and 60.5% (95% CI 52.3—68.6), respectively.[9] A report on a global perspective on PZA resistance showed that approximately 16% of TB cases are associated with PZA-resistant isolates.[26] Specifically, the PZA resistance rate was 2%—7.5% in non-MDR-TB and 36%—85% in MDR-TB cases.[27,28] A hospital-based study conducted in Southern Taiwan showed that the PZA resistance rate was 30% in 55 MDR-TB cases.[29] In addition, a previous study revealed that PZA resistance was significantly associated with RIF resistance and that the burden of PZA resistance could be estimated.[30]

Furthermore, we found that the cross-resistance ratio between RIF and RBT was 85.1%, which is higher than 72.7% in Japan and 72.2% in Canada and comparable to 85.9% in China.[31—33] Special attention must be given to second-line drugs, including ETH, due to the frequency of cross-resistance between INH and ETH by mutations in *inhA* or its promoter that were detected in 30.1% of *M. tuberculosis* isolates from Taiwan and 33.3% from Colombia.[34]

In 2013, surveillance of resistance to FQs and PZA was initiated in 5 countries, including Azerbaijan, Bangladesh, Belarus, Pakistan and South Africa. Preliminary results revealed that resistance to RIF is often associated with resistance to PZA. Moreover, resistance to OFX is generally lower than RIF resistance, except in Asian countries where FQs are extensively used.[18] In this survey, the ratios of resistance to FQs (9.0%—14.1%) were higher than those of SLIDs (4.1%—7.1%). We observed a decreasing trend in resistance to OFX, MFX, SLIDs, RBT, ETH and PAS in new MDR-TB cases. Nevertheless, an increasing trend was found in resistance to LFX (APC = +7.9%) in new cases and to AMK (APC = +3.3%) and CAP (APC = +5.3%) in previously treated cases. A policy to restrict the prescription of FQs has been implemented since 2007,[6] even though a significant decrease was found in resistance to OFX (APC = −24.6%) and MFX (APC = −23.3%); the increasing trend of LFX resistance warrants further investigation.

In summary, we reported results of drug-resistance surveillance of MDR-TB in Taiwan from 2008 to 2019. The surveillance system has been strengthened due to the quality assured universal DST program since 2007. We observed significant declines in both new TB and MDR-TB cases. The decreasing incidence of MDR-TB was most prominent among those who had been previously treated. Efforts for the decreasing incidence of previously treated MDR-TB in Taiwan might include directly observed treatment, short course (DOTS) strategy, timely and comprehensive DST services, and diligent case management program. Nevertheless, the slow decreasing trend of new MDR-TB cases remains a challenge for the DR-TB management program. Of note, low FQs resistant rate indicating a *FQ*-based short-course regimen for DR-TB and a FQ-based regimen for contacts with presumed DR-TB infection are feasible. The findings could inform National TB program to develop integrate strategies for guiding procurement of drugs, for updating treatment regimens and designing diagnostic algorithms. Continuous surveillance of drug resistance is crucial for understanding the burden of drug-resistant TB and for preparing effective responses for TB elimination.

Institutional Review Board and informed consent statement

Information on vital status was obtained from the National Surveillance Network of Communicable Diseases of Taiwan. The study was approved by the Institutional Review Board of the Centers for Disease Control, Ministry of Health and Welfare (TwCDC IRB No. 109205). The study only reviewed the TB Registry, and written informed consent of the participants was waived.

Conflict of interest

None.

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