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Characteristics and Trend of Drug-Resistant Tuberculosis at a Major Specialized Hospital in Chongqing, China: 2016 Versus 2019

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Original Research

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Abstract

Objective: The epidemic of drug-resistant tuberculosis (DR-TB) has become a major concern in global TB control. This study aimed to investigate the patterns and trend of DR-TB epidemic between different time periods in Chongqing.

Methods: A total of 985 and 835 culture positive TB patients with drug susceptibility testing (DST) results admitted to the hospital in 2016 and 2019, respectively, were included. Chi-square testing was used to compare the prevalence and trends of DR-TB in 2016 and 2019.

Results: The proportion of previously treated TB cases with culture positivity was 45.7% in 2019, significantly higher than that in 2016 (39.1%, $P = 0.004$). The overall rate of drug resistance in 2019 was 43.1%, higher than that in 2016 (40.2%). The rates of multi-drug resistant TB (MDR-TB) and pre-extensively drug resistant TB (pre-XDR-TB) increased significantly from 2016 to 2019 among all TB cases (MDR: 25% vs 33.4%, $P < 0.001$ and pre-XDR: 7.1% vs 12.8%, $P < 0.001$, respectively) and previously treated TB cases (MDR: 46.5% vs 56%, $P = 0.008$ and pre-XDR: 13.2% vs 21.5%, $P = 0.003$, respectively).

Conclusions: Our findings indicated that the prevalence of DR-TB remains high in Chongqing. The trend of resistance to anti-TB drugs beccame worse between 2016 and 2019. Moreover, acquired MDR may play a major role in MDR-TB epidemic in Chongqing. Therefore, rapid diagnosis and effective treatment of TB patients will be important to reduce the burden of DR-TB in Chongqing.

Drug-resistant tuberculosis (DR-TB), especially multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), remains a serious public health issue worldwide. According to the World Health Organization (WHO) Global TB Report 2020, an estimated 10.0 million people fell ill with TB in 2019 globally, and close to half a million people developed rifampicin-resistant tuberculosis (RR-TB).[1] China, which is one of the 30 high TB burden countries, had the world's second largest number of RR-TB/MDR-TB cases, accounting for 14% of the global total, behind only India (RR/MDR-TB, 27%).[1] Based on the 2007 national survey of DR-TB in China, 5.7% of new cases and 25.6% of previously treated cases had MDR-TB, and there were about 120 000 new cases of MDR-TB in China per year.[2] The national survey in 2010 estimated that the proportion of MDR-TB cases was 6.8% among total incident TB cases.[3] MDR-TB is a disaster, as the treatment of MDR-TB patients is complex and has a lower success rate. MDR-TB patients should take drugs that are more expensive and have more serious side effects, and also accompanied by a longer treatment period (18–24 months). However, only 57% RR/MDR-TB patients successfully completed treatment in 2019.[1] Therefore, the proportion of DR/MDR-TB cases can be a useful indicator for evaluating the performance of a TB control program. A high proportion of DR/MDR-TB is usually related to poor TB treatment and management. However, little is known about the current prevalence of DR/MDR-TB in Chongqing, China.

Assessment of temporal trends in drug resistance will be useful for strengthening TB control measures. Few studies have evaluated the trends in drug resistance among TB patients. The trend of DR-TB and MDR-TB declined from 2008 to 2015 in Guizhou, China.[4] Moreover, a study from Dalian, China, showed significant downtrends for the rate of MDR-TB from 2012 to 2019.[5] The total rate of DR-TB among new cases showed a downward trend in Shangdong, China, from 2004 to 2018,[6] while the proportion of MDR-TB increased among primary TB cases during 2004 to 2019.[7] In Chongqing, the drug-resistance rate of rifampicin (RFP)

increased from 2010 to 2017.[8] However, the current prevalence trend of DR-TB, especially MDR/XDR-TB, in Chongqing, is still poorly known.

Chongqing is the only municipality directly under the central government in southwest China with 33 million residents. About 23 000 TB patients were reported, and the TB notification rate was 73.37 cases per 100 000 population in 2018. Chongqing is a city with high incidence of both TB and MDR-TB,[9] and the incidence of TB ranked eight in China in 2018. As drug resistance of TB shows geographic variation, investigation of the patterns and trend of DR-TB could help to know the situation of DR-TB and to make appropriate adjustments of the TB control strategy in this region. This study tried to investigate the patterns and prevalent trend of drug resistance between 2016 and 2019, based on the results of drug susceptibility testing (DST). Our study is envisaged to be useful in planning effective intervention strategies for the control of DR-TB in this region and other regions with similar situations.

Methods

Study Design and Population

This study was conducted at the Chongqing Public Health Medical Center, which is a class A, grade 3 hospital for infectious diseases in southwest China. It is the biggest specialized hospital in Chongqing with a 800-bed TB center for the treatment of TB and DR-TB patients. All culture positive TB patients with DST results who admitted to the hospital in 2016 and 2019 were included in this study. Patients infected with nontuberculous mycobacteria were excluded. In 2016, 8434 suspected TB patients were tested with a TB culture and 2756 patients were culture positive, in which 868 patients were excluded because of NTM infection or no DST results. Of the remaining 1888 TB patients, 985 were inpatients. In 2019, 13 785 suspected TB patients were tested with a TB culture and 4365 patients were culture positive, in which 1372 patients were excluded because of NTM infection or no DST results. Of the remaining 2993 TB patients, 835 were inpatients. The medical records were reviewed for demographic information, clinical characteristics, and laboratory results. The highest value was selected for analysis if patients had multiple results of DST.

Culture and Drug Susceptibility Testing

The clinical specimens from suspected TB patients were collected for preparing acid-fast bacillus smear. The specimens were further cultured using the Löwenstein–Jensen medium according to procedures recommended by the WHO.[10] The positive culture organisms were tested for the expression of MPT64 protein, which is the main protein secreted by TB. The suspected NTM colonies, which were MPT64-negative, were excluded. DST for TB strains was performed using the proportion method on Löwenstein–Jensen medium, with the following concentrations of anti-TB drugs: isoniazid (INH), 0.2 μg/ml; RFP, 40 μg/ml; streptomycin (STR), 4.0 μg/ml; ethambutol (EMB), 2.0 μg/ml; levofloxacin (LFX), 2.0 μg/ml; amikacin (AMK), 30.0 μg/ml; and capreomycin (CAP), 40.0μg/ml. TB strains were deemed to be resistant to a specific drug when the growth rate was ≥ 1% that of the control. The standard strain H37Rv was used as an internal quality control and included for each batch of culture.

Definitions

Drug resistance was defined as resistance to at least one of the aforementioned anti-TB drugs. MDR-TB was defined as TB resistance to at least RFP and INH. Pre-XDR-TB was defined as TB resistance to RFP, INH, and either the fluoroquinolones (LFX) or one of the injectable second-line anti-TB drugs (AMK and CAP), but not both. XDR-TB was defined as TB resistance to at least RFP and INH, as well as any fluoroquinolone and at least one of the injectable second-line anti-TB drugs. New cases were defined as case patients who had never been previously treated for TB or had taken anti-TB drugs for less than 1 month. Previously treated TB cases were defined as case patients who had received 1 month or more of anti-TB drugs before the current TB episode, either a true relapse or a new episode of TB caused by reinfection.[11]

Statistical Analysis

The statistical analysis was conducted with SPSS 12.0 software (IBM SPSS Statistics for Windows, Version 17.0; SPSS Inc., Chicago, USA). A univariate analysis of categorical variables was performed with the chi-square test or Fisher's exact test as appropriate. Chi-square test was used to compare drug resistance rates between new and previously treated cases and between isolates collected in 2016 and 2019. Statistically significant differences were considered when the P-value was < 0.05.

Study Approval

This study was approved by the Ethics Committee of Chongqing Public Health Medical Center. The ethics committee waived the requirement for written informed consent as all patient information used in this study had been routinely collected and was analyzed anonymously.

Results

Demographic Characteristics of TB Patients

A total of 1820 culture-positive TB patients with DST results who admitted to the hospital were analyzed, including 985 and 835 TB cases from 2016 and 2019, respectively. The proportion of culture-positive TB patients was 32.7% (2756/8434) in 2016 and 31.7% (4365/13785) in 2019 (Figure 1). Ages of the patients ranged from 8 to 87 years in 2016, and 13 to 90 years in 2019. As shown in Table 1, the proportion of TB patients with culture positivity who were ≥ 45 years old was higher in 2019 (55.1%) than that in 2016 (49.2%). The male-to-female ratio was 2.6 and 2.8 in 2016 and 2019, respectively. Farmers were more likely to have TB, and increased proportions were observed in 2019 (57.4%) compared to 2016 (45.2%). The proportion of smoking TB patients with culture positivity in 2019 (53.8%) was significantly higher than that in 2016 (47.9%), as well as the proportion of smear positive TB cases (62.9% in 2019 and 57.2% in 2016). Of note, the proportion of previously treated cases in 2019 (45.7%) was significantly higher compared to that in 2016 (39.1%).

TB Drug Resistance Pattern in 2016 and 2019

Among the 1820 TB cases with culture positivity, the overall rate of resistance to any examined drug in the TB strains increased from 40.2% in 2016 to 43.1% in 2019. INH had the highest rate of drug resistance in both 2016 (33.4%) and 2019 (38.8%), followed by RFP

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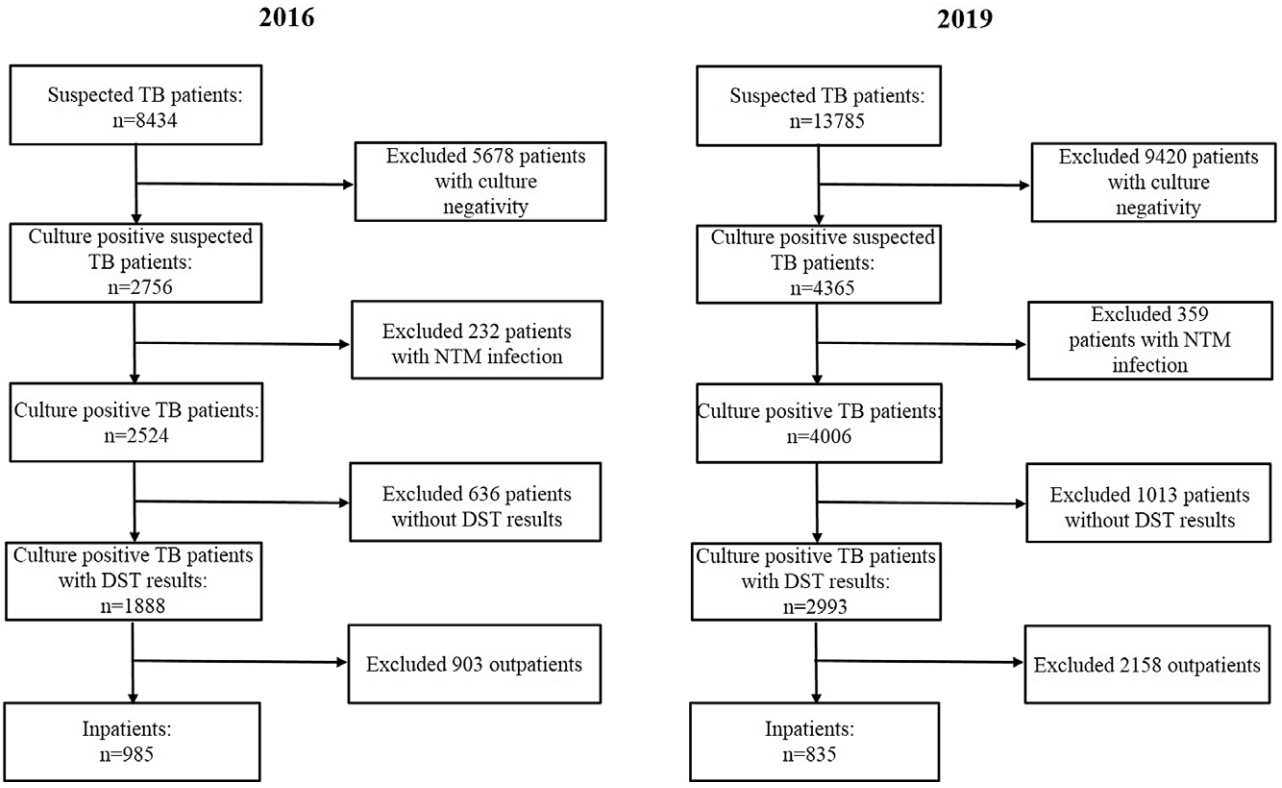

Figure 1. Study population of TB inpatients in Chongqing in 2016 and 2019.

(28.0% in 2016 and 35.2% in 2019), STR (26.8% in 2016 and 32.7% in 2019), and EMB (18.1% in 2016 and 24.0% in 2019). In 2016, about 16.4% (162/985) TB cases with culture positivity were resistant to all the 4 first-line anti-TB drugs, while the proportion was 20.8% (174/835) in 2019. The overall rates of MDR-TB (33.4%), pre-XDR-TB (12.8%), and XDR-TB (3.4%) in 2019 were higher than those in 2016 (25.0%, 7.1%, and 2.3%, respectively). The common combinations of MDR-TB were INH with RFP or STR. The rates of resistance to second-line anti-TB drugs (LFX, AMK, and CAP) in 2019 (13.2%, 6.6%, and 4.4%, respectively) were higher than those in 2016 (8.3%, 5.1%, and 4.2%, respectively). The details are shown in Table 2.

The proportion of resistance to any individual or multiple anti-TB drugs in previously treated cases was significantly higher than that in new cases in both 2016 and 2019 (Table 3). In both 2016 and 2019, the proportions of resistance to the first- and second-line anti-TB drugs increased 3 to 4 times in previously treated patients compared to new cases, as well as the rates of MDR-TB, pre-XDR-TB, and XDR-TB. The details are shown in Table 3.

Trend of Drug Resistance Between 2016 and 2019

As shown in Table 4, a significant higher proportion of resistance to INH ($P = 0.017$), RFP ($P < 0.001$), STR ($P = 0.006$), EMB ($P = 0.002$), and second-line anti-TB drugs ($P = 0.008$) was observed among all TB patients with culture positivity in 2019. Furthermore, there were significantly higher proportions of resistance to RFP ($P = 0.045$), EMB ($P = 0.012$), and second-line anti-TB drugs ($P = 0.004$) among previously treated cases in 2019. The rates of MDR-TB and pre-XDR-TB were also higher among all TB cases ($P < 0.001$ and $P < 0.001$, respectively) and previously treated TB cases with culture positivity ($P = 0.008$ and $P = 0.003$, respectively) in 2019, but no significant changes were observed among new TB cases with culture positivity ($P = 0.123$ and $P = 0.059$, respectively). The rates of resistance to any first-line drugs and XDR-TB were comparable among either new cases ($P = 0.527$ and $P = 0.990$, respectively) or previously treated cases with culture positivity ($P = 0.657$ and $P = 0.229$, respectively) between 2016 and 2019. Notably, there was a slight decline in resistance to any second-line anti-TB drugs among new cases with culture positivity in 2019 compared to 2016 ($P = 0.650$). Overall, the rates of resistance to any individual or multiple anti-TB drugs were higher in 2019 than those in 2016, with the exception of the resistance rate of the second-line anti-TB drugs among new TB cases with culture positivity.

Discussion

In this hospital-based study, 1820 culture positive TB patients with DST results admitted to the hospital in 2016 and 2019 were included to evaluate the patterns and temporal trend of resistance to anti-TB drugs. The percentage of previously treated TB cases increased significantly from 39.1% in 2016 to 45.7% in 2019. Furthermore, the rates of resistance to any individual or multiple anti-TB drugs increased among either new cases or previously treated cases between 2016 and 2019, except the rate of resistance to second-line drugs among new cases, which declined between 2016 and 2019. These results reflect a severe and worsening situation of DR-TB epidemic in Chongqing.

About two-thirds of TB patients with culture positivity were in the age groups of 25–44 years and 45–64 years in both 2016 and 2019, suggesting that TB prevention and control in Chongqing should focus more on these patients. This finding

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Table 1. Comparison in demographic and clinical characteristics of culture positive TB patients who had DST results collected in 2016 and 2019

Characteristics	2016 (n = 985, n/%)	2019 (n = 835, n/%)	*P* value
Age group (years)			0.029
0-14	9 (0.9)	5 (0.6)	
15-24	185 (18.8)	119 (14.3)	
25-44	306 (31.1)	251 (30.1)	
45-64	366 (37.2)	332 (39.8)	
≥ 65	118 (12.0)	128 (15.3)	
Gender			0.424
Male	709 (72.0)	615 (73.7)	
Female	276 (28.0)	220 (26.3)	
Occupation			< 0.001
Farmer	445 (45.2)	479 (57.4)	
Worker	232 (23.6)	117 (14.0)	
Student	87 (8.8)	47 (5.6)	
Others	221 (22.4)	192 (23.0)	
Stability of residence			0.480
Permanent resident	782 (79.4)	674 (80.7)	
Migrant/temporary resident	203 (20.6)	161 (19.3)	
Smoking			0.013
Yes	472 (47.9)	449 (53.8)	
No	513 (52.1)	386 (46.2)	
Hemoptysis at diagnosis			< 0.001
Yes	268 (27.2)	150 (18.0)	
No	717 (72.8)	685 (82.0)	
Coexisting diseases			0.324
Diabetes	137 (13.9)	124 (14.9)	
Hepatitis B	78 (7.9)	90 (10.8)	
AIDS	69 (7.0)	81 (9.7)	
Sputum smear			0.013
Positive	563 (57.2)	525 (62.9)	
Negative	422 (42.8)	310 (37.1)	
Treatment history			0.004
New cases	600 (60.9)	453 (54.3)	
Treated cases	385 (39.1)	382 (45.7)	

AIDS, acquired immune deficiency syndrome; TB, tuberculosis.

Table 2. Drug resistance patterns of TB patients with culture positivity collected in 2016 and 2019

Type of TB resistance	2016 (n = 985, n/%)	2019 (n = 835, n/%)
Any drug-resistance	396 (40.2)	360 (43.1)
Resistance to any first-line drugs	379 (38.5)	357 (42.8)
Resistance to individual drugs in any test		
INH	329 (33.4)	324 (38.8)
RFP	276 (28.0)	294 (35.2)
STR	264 (26.8)	273 (32.7)
EMB	178 (18.1)	200 (24.0)
LFX	82 (8.3)	110 (13.2)
AMK	50 (5.1)	55 (6.6)
CAP	41 (4.2)	37 (4.4)
Resistance to single-drug only		
(INH/ RFP/ STR/ EMB/ LFX)	82 (8.3)	53 (6.3)
Resistance to 2 drugs		
RFP+INH	37 (3.8)	19 (2.3)
INH+STR	30 (3.0)	11 (1.3)
Others	21 (2.1)	11 (1.3)
Resistance to 3 drugs		
RFP+INH+STR	99 (10.1)	50 (6.0)
Others	21 (2.1)	18 (2.2)
Resistance to 4 drugs		
RFP+INH+STR+EMB	72 (7.3)	67 (8.0)
Others	44 (4.5)	18 (2.2)
Resistance to 5 drugs		
RFP+INH+STR+EMB+LFX	65 (6.6)	61 (7.3)
Others	9 (0.9)	13 (1.6)
Resistance to 6 drugs		
RFP+INH+STR+EMB+LFX+AMK/CAP	9 (0.9)	10 (1.2)
RFP+INH+STR+EMB/LFX+AMK+CAP	6 (0.6)	14 (1.7)
Resistance to 7 drugs		
RFP+INH+STR+EMB+LFX+AMK+CAP	9 (0.9)	14 (1.7)
MDR	246 (25.0)	279 (33.4)
Pre-XDR	70 (7.1)	107 (12.8)
XDR	23 (2.3)	28 (3.4)

AMK, amikacin; CAP, capreomycin; EMB, ethambutol; INH, isoniazid; LFX, levofloxacin; MDR, multi-drug resistance; RFP, rifampicin; STR, streptomycin; TB, tuberculosis; XDR, extensively drug resistance.

was consistent with previous studies, in which TB prevalence was mostly observed in young and middle aged patients.[4,6] Furthermore, TB affects men more frequently than women, which were almost twice higher compared with female TB patients in our study. This gender difference has also been reported by the national survey of China.[12] The WHO TB Report 2020 also indicated that the highest TB burden was among adult men, accounting for 56% of all TB cases in 2019.[1] Moreover, TB incidence was more frequently observed in farmers in both 2016 and 2019 in our study. These differences of TB incidence observed in our study may be related to the socioeconomic condition of TB patients. Evidences had indicated that TB was closely associated with poverty.[13] Chongqing has large, poor, rural populations (mostly farmers), and many adult men have to go out for a living. Thus, the lower socioeconomic status may relate to the higher TB incidence in Chongqing. In this study, the smear negative but culture positive TB cases accounted for a large proportion in both 2016 and 2019. Although sputum smear-positive patients were more infectious, a previous study has indicated that 17% of TB transmission were due to sputum smear negative but culture positive TB patients.[14] Moreover, smear negative patients may be delayed in diagnosis and initiation of treatment, and may result in further TB transmission. In addition, the proportion of previously treated TB cases with culture positivity was significantly higher in 2019 in this study, implying that the treatment and management of previously treated TB cases with culture positivity are still a big challenge for TB control in Chongqing. Previous treatment is a well-known risk factor for the incidence of DR-TB. In this study, rates of resistance to any individual or

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Table 3. Comparison of drug resistance in new and previously treated TB patiens with culture positivity collected in 2016 and 2019

	2016 (n = 985)			2019 (n = 835)		
Type of drug resistance	New cases (n = 600, n/%)	Treated cases (n = 385, n/%)	*P* value	New cases (n = 453, n/%)	Treated cases (n = 382, n/%)	*P* value
Resistance to any first-line drugs	137 (22.8)	242 (62.9)	< 0.001	111 (24.5)	246 (64.4)	< 0.001
INH	111 (18.5)	218 (56.6)	< 0.001	92 (20.3)	232 (60.7)	< 0.001
RFP	80 (13.3)	196 (50.9)	< 0.001	72 (15.9)	222 (58.1)	< 0.001
STR	91 (15.2)	173 (44.9)	< 0.001	84 (18.5)	189 (49.5)	< 0.001
EMB	61 (10.2)	117 (30.4)	< 0.001	51 (11.3)	149 (39.0)	< 0.001
LFX	36 (6.0)	46 (11.9)	< 0.001	22 (4.9)	88 (23.0)	< 0.001
AMK	19 (3.2)	31 (8.1)	< 0.001	15 (3.3)	40 (10.5)	< 0.001
CAP	16 (2.7)	25 (6.5)	0.003	10 (2.2)	27 (7.1)	< 0.001
MDR	67 (11.2)	179 (46.5)	< 0.001	65 (14.3)	214 (56.0)	< 0.001
Pre-XDR	19 (3.2)	51 (13.2)	< 0.001	25 (5.5)	82 (21.5)	< 0.001
XDR	8 (1.3)	15 (3.9)	0.009	6 (1.3)	22 (5.8)	< 0.001
Resistance to any second-line drugs	51 (8.5)	77 (20.0)	< 0.001	35 (7.7)	111 (29.1)	< 0.001

AMK, amikacin; CAP, capreomycin; EMB, ethambutol; INH, isoniazid; LFX, levofloxacin; MDR, multi-drug resistance; RFP, rifampicin; STR, streptomycin; TB, tuberculosis; XDR, extensively drug resistance.

Table 4. Trend in prevalence of drug resistance among TB patients with culture positivity collected in 2016 and 2019

Type of drug resistance	Treated history	2016 (%, n)	2019 (%, n)	*P* value
Resistance to any first-line drugs	All	38.5 (379/985)	42.8 (357/835)	0.064
	New cases	22.8 (137/600)	24.5 (111/453)	0.527
	Treated cases	62.9 (242/385)	64.4 (246/382)	0.657
INH	All	33.4 (329/985)	38.8 (324/835)	0.017
	New cases	18.5 (111/600)	20.3 (92/453)	0.461
	Treated cases	56.6 (218/385)	60.7 (232/382)	0.248
RFP	All	28.0 (276/985)	35.2 (294/835)	0.001
	New cases	13.3 (80/600)	15.9 (72/453)	0.242
	Treated cases	50.9 (196/385)	58.1 (222/382)	0.045
STR	All	26.8 (264/985)	32.7 (273/835)	0.006
	New cases	15.2 (91/600)	18.5 (84/453)	0.145
	Treated cases	44.9 (173/385)	49.5 (189/382)	0.208
EMB	All	18.1 (178/985)	24.0 (200/835)	0.002
	New cases	10.2 (61/600)	11.3 (51/453)	0.569
	Treated cases	30.4 (117/385)	39.0 (149/382)	0.012
Resistance to any second-line drugs	All	13.0 (128/985)	17.5 (146/835)	0.008
	New cases	8.5 (51/600)	7.7 (35/453)	0.650
	Treated cases	20 (77/385)	29.1 (111/382)	0.004
MDR	All	25.0 (246/985)	33.4 (279/835)	< 0.001
	New cases	11.2 (67/600)	14.3 (65/453)	0.123
	Treated cases	46.5 (179/385)	56.0 (214/382)	0.008
Pre-XDR	All	7.1 (70/985)	12.8 (107/835)	< 0.001
	New cases	3.2 (19/600)	5.5 (25/453)	0.059
	Treated cases	13.2 (51/385)	21.5 (82/382)	0.003
XDR	All	2.3 (23/985)	3.4 (28/835)	0.190
	New cases	1.3 (8/600)	1.3 (6/453)	0.990
	Treated cases	3.9 (15/385)	5.8 (22/382)	0.229

EMB, ethambutol; INH, isoniazid; MDR, multi-drug resistance; RFP, rifampicin; STR, streptomycin; TB, tuberculosis; XDR, extensively drug resistance.

multiple anti-TB drugs among previously treated cases were mostly 3 to 4 times higher than those among new cases. Therefore, the implementation of an effective strategy, such as the directly observed treatment short-course, still plays an important role in controlling the incidence of DR-TB, especially in terms of supervising patients to complete the treatment.

The current study demonstrated the existence of many drug-resistance patterns among DR-TB patients with culture positivity in Chongqing. Moreover, a higher proportion of TB patients was resistant to 5 or more anti-TB drugs in 2019 (13.5% in 2019 and 9.9% in 2016), and most TB patients with culture positivity were resistant to all the 4 first-line anti-TB drugs. Furthermore, about

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37.8% (93/246) MDR-TB patients in 2016 and 48.4% (135/279) MDR-TB patients in 2019 were either pre-XDR-TB or XDR-TB, higher than results from Guizhou Province of China (36.3%).[4] These results indicated that it is more difficult for the treatment of DR-TB with the constant using of "old" anti-TB drugs. Thus, new anti-TB drugs are urgently needed, such as bedaquiline, which was recommended by the WHO in 2019.[15] Bedaquiline showed a good effect for the treatment of MDR-TB.[16] However, TB patients with resistance to bedaquiline have been observed in various regions.[17–21] Thus, more attention should be paid to avoid resistance to new anti-TB drugs. In addition, individualized treatment regimens based on DST results should be made to avoid the generation of further resistance.

The time trend of the prevalence of DR-TB in Chongqing between 2016 and 2019 was analyzed. Previous studies have shown that an increasing or persistantly high prevalence of DR-TB was observed in mainland China.[22,23] Consistently, increased trend of drug resistance to any individual or multiple anti-TB drugs was observed in this study, except the resistance to second-line anti-TB drugs among new TB cases. Many reasons may account for the increased prevalence of DR-TB in Chongqing. First, as mentioned before, the socioeconomic and demographic characteristics may influence the incidence of TB and DR-TB. The national survey indicated that the western region of China had the highest TB prevalence.[12] Chongqing is located in southwest China and contains 39 districts and counties, of which 14 were state-level, poverty-stricken areas with a high incidence of TB.[24] The lower socioeconomic status and weakness of the health resource may result in the increased prevalence of DR-TB in Chongqing. Thus, increased financial and policy support is extremely important to prevent the prevalence of TB and DR-TB in Chongqing.

Second, the inappropriate treatment and management of TB patients may result in the increased prevalence of DR-TB in Chongqing. Normally, drug resistance among new TB cases is caused by transmission, while drug-resistance among previously treated patients could be acquired resistance due to inappropriate treatment, and also could be the direct transmission of DR-TB. In our study, the increased resistance to RFP, EMB, and second-line anti-TB drugs, as well as MDR-TB and pre-XDR-TB, was statistically significant among previously treated patients, but only slightly increased among new cases. Furthermore, about 72.8% and 76.7% of the MDR-TB patients with culture positivity were from previously treated TB cases in 2016 and 2019, respectively. These findings indicated that acquired DR/MDR-TB may play a very important role and far outweigh primary DR/MDR-TB in the DR/MDR-TB epidemic in Chongqing. Therefore, distinguishing the cause of DR-TB prevalence among previously treated patients is important for making a reasonable strategy to prevent DR-TB epidemic in Chongqing. However, it is still unclear as a genotyping analysis of these DR-TB strains was not performed in this study. Genotyping analysis, such as variable number tandem repeats and whole genome sequencing, has been proved to be an effective method to identify the cause of DR-TB incidence, resulting from inadequate therapy or infection with a DR-TB strain. Previous studies have indicated that exogenous reinfection was the main cause of DR-TB incidence among previously treated patients by genotyping analysis.[25,26] Furthermore, recent transmission of MDR-TB strains contributed mostly to the MDR-TB epidemic in China.[27,28] Thus, further genotyping analysis of these DR-TB strains is urgently needed in Chongqing. We suggest more emphasis should be paid on the standard and effective treatment of TB patients, so as to reduce the prevalence of DR-TB due to inadequate therapy. Meanwhile, effective management of DR-TB patients is extremely important in terms of decreasing the DR-TB transmission. Mask-wearing was regarded as an effective method to reduce the infectiousness of patients with TB and should be retained as a strategy for TB control.[29]

Third, the introduction of rapid molecular diagnosis and the increased reimbursement rate of medical insurance may be related to the increased DR/MDR-TB epidemic in Chongqing. With the expanded scope of RR-TB screening and the application of rapid molecular diagnosis equipment, an increased number of RR-TB patients was notified. Further screening of MDR-TB patients among RR-TB paitents is mandatory in China, which will be a benefit for the effective treatment of MDR-TB patients. Moreover, more TB-suspected patients would like to screen for TB or MDR-TB, as the reimbursement rate of medical insurance has been increased for TB patients. With the increase in TB case finding, the following standardized treatment and management of these patients will be extremely crucial for the control of DR-TB epidemic in Chongqing.

Limitations

The current study has several limitations. First, all the patients were from a single designated hospital for DR-TB in Chongqing, and were hospitalized patients with relatively serious symptoms. Thus, the rate of drug resistance may be overestimated. Despite this, the trend of drug resistance between 2016 and 2019 could give a better understanding of the prevalence characteristics of drug resistance and could help make reasonable regimens for TB control in Chongqing. Second, the outcome information about TB patients' treatment cannot be provided, because of different functions between the hospital system and TB disease control system. In China, TB hospital is mainly responsible for the treatment of TB patients, while the TB disease control system is mainly responsible for the management of TB patients. Third, our study only included TB patients with culture positivity, and attention should also be paid to TB patients with culture negativity, which account for about 20% of pulmonary TB cases.[30] Fourth, we did not do genotyping analysis of the DR/MDR-TB isolates. Thus, the cause of DR/MDR-TB incidence among previously treated TB patients in Chongqing warrants further investigation.

Conclusions

We demonstrated an increasing trend of DR/MDR-TB epidemic between 2016 and 2019 in Chongqing, indicating a worsening situation of drug resistance among TB patients with culture positivity and a great challenge to meet the WHO's end TB strategy.[31] Our findings indicated that acquired MDR-TB may be the main cause of the MDR-TB epidemic in Chongqing. Furthermore, DST for both first- and second-line anti-TB drugs is urgently needed for making individualized anti-TB regimens. In summary, with the increment of drug resistance rate in Chongqing, more efforts are needed to enhance the diagnosis, treatment, and management of TB patients, especially DR-TB patients.

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