Infection and Drug Resistance

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ORIGINAL RESEARCH

Determining *Mycobacterium tuberculosis* Drug Resistance and Risk Factors for Multidrug-Resistant Tuberculosis in Sputum Smear-Positive Tuberculosis Outpatients in Anhui Province, China, 2015–2016

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Background: Multidrug-resistant tuberculosis (MDR-TB) is currently a major problem in China. The prevention and treatment work for MDR-TB patients started late in Anhui province. To determine the prevalence of MDR-TB in sputum smear-positive TB patients (SSPTBPs) and analyze the risk factors for MDR-TB in Anhui province, we conducted an investigation of drug resistance among SSPTB outpatients from September 2015 to August 2016.

Methods: A stratified cluster-randomized sampling method was used to obtain a representative sample. It was estimated that 2290 new cases and 440 previously treated cases of SSPTBPs needed to be recruited from 40 survey sites. Isolates were tested for resistance to six first-line and second-line anti-TB drugs. Information from patient questionnaire survey was used to identify factors linked to MDR-TB.

Results: Finally, a total of 3047 SSPTBPs were recruited from 40 survey sites; of these, 2530 specimens were successfully cultured and had drug susceptibility testing done. The proportions of rifampin resistant (RR)-TB were 11.42% (289/2530, 95% CI: 10.18–12.66%), 7.64% (163/2133, 95% CI: 6.38–8.62%) and 31.74% (126/397, 95% CI: 27.38–36.60%) in all cases, new cases and previously treated cases, respectively, and the proportions of confirmed MDR-TB were 7.63% (193/2530, 95% CI: 6.59–8.66%), 4.97% (106/2133, 95% CI: 4.05–5.89%) and 21.91% (87/397, 95% CI: 17.83–26.00%), respectively. The ofloxacin resistance rate in previously treated SSPTBPs reached 21.66% (95% CI: 17.33–26.75%). Patients who had received two or more anti-TB treatment courses were significantly associated with MDR-TB compared to patients who have received one anti-TB course.

Conclusion: MDR-TB prevalence was high among SSPTBPs in Anhui province, and past anti-TB treatment course was associated with MDR-TB.

Keywords: drug resistance, multidrug-resistant, *Mycobacterium tuberculosis*, tuberculosis

Background

Multidrug-resistant tuberculosis (MDR-TB) is a major problem in global TB control. In 2017, there were an estimated 558,000 new cases of rifampin (RIF) resistant TB (RR-TB), and 82% of which were MDR-TB.[1] India, China and the Russian Federation accounted for almost half of the world's cases of MDR/RR-TB, and there were about 58,000 new cases of MDR/RR-TB in China.[1]

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Anhui province is located in the eastern part of mainland China, with a jurisdiction area of 140,100 square kilometers. At the end of 2017, the resident population was 62.548 million, and the per capita gross domestic product was 6200 dollars. Since 2004, a TB network monitoring system covering the whole province has been gradually established. 33,607 people with TB were reported in 2017, including 10,341 sputum smear-positive TB patients (SSPTBPs) (The data were obtained from the China TB network surveillance system).

The prevention and treatment work for MDR-TB patients started late in Anhui province. In 2012, the prevention and treatment of MDR-TB patients were carried out in Anqing, Fuyang and Ma'anshan city by relying on the Global Fund Program.[2] After two years, the diagnosis and management of MDR-TB were officially launched in this province. When the Global Fund Program ended in 2016, the screening of MDR-TB patients was low with only 278 MDR-TB patients reported through the network. Historically, Anhui province participated in the 4 national TB epidemiological surveys. Since Anhui province was only a site in the national sample survey, and the sample size and sampling design mainly focused on the representativeness of TB prevalence in general, the obtained drug resistance results were not representative of the actual drug resistance level. In addition, a nationwide drug resistance baseline survey was conducted in 2007; these results showed MDR-TB prevalence rate in all TB patients, new TB patients and previously treated TB patients was 8.32% (401/3929), 5.71% (175/3037), and 25.64% (226/892), respectively.[3] Since only 4 survey sites were set up in Anhui province, the results did not reflect the overall situation of Anhui province.

Domestic and foreign research reports indicated MDR-TB was closely related to a number of factors such as sociodemographic factors, economic level, and past anti-TB treatment courses,[4–14] and these factors may differ by region or country. MDR-TB risk factors were not yet determined in Anhui province.[15] The TB Prevention and Treatment Institute of Anhui province conducted a study to determine the prevalence of MDR-TB and analyzed the risk factors for MDR-TB in Anhui province.

Methods

In 2015, there were 86 TB clinics in Anhui province, covering 105 counties (districts) in 16 cities. It is estimated that in 2015, the prevalence of HIV among the entire population and TB patients in our province was 0.16% and 0.02% (102/35,550), which are all in a low epidemic situation. We did a prospective study from 2015 to 2016, and HIV was not test.

Sampling Method

(1) A stratified cluster sampling method was used to obtain a representative sample by referring to the monitoring program of the World Health Organization (WHO) Guidelines for surveillance of drug resistance in tuberculosis (Fourth Edition).[16]

2) We only chose sputum smear-positive specimens for culture, because the possibility of positive culture was very low for sputum smear-negative specimens, and subsequent drug sensitivity testing (DST) cannot be carried out.

3) The sample size is calculated according to the statistical requirements of the cross-sectional survey. Sample size formula: n= deff* (N*z^2 p(1-p))/(d^2 (N-1)+z^2 p (1-p)), where parameter N, the total number of SSPTBPs reported in the past year, was estimated according to the number in 2014 (N=11,151). The estimated resistance rate of RIF in new cases and previously treated cases was 0.07 (p=0.07), accuracy d=±1.4% and 0.3 (p=0.3), accuracy d= ±6%, respectively, credibility was set to 95%, z=1.96, design effect deff=2.[3,16] Then the sample size required for new cases of SSPTBPs is 2290, and the sample size required for previously treated cases is 440.

4) After comprehensive consideration of the sample size required for this survey, the time limit for completing the survey within one year and the number of TB patients actually diagnosed and treated at each survey site each year, 40 survey sites were finally selected. Then each survey site should recruit 57 new cases and 11 previously treated cases of SSPTBPs.

5) For stratified cluster sampling, the units of sampling are city-level or county-level (district-level) TB diagnosis and treatment units, mainly including city-level, county-level (district-level) disease prevention and control centers and TB designated hospitals.

6) Specific steps for sampling (Figure 1). Step 1 is to sort the administrative division code of TB prevention and control planning units in Anhui province. Step 2 is to collect the number of SSPTBPs registered and reported by all TB prevention and treatment planning implementation units in 2014, and list the cumulative number of SSPTBPs. Step 3 is to determine the sampling interval, which is equal to the cumulative number of SSPTBPs divided by the number of units to be sampled. Step 4 is to use the random number table to generate a random number, and the planning unit corresponding to the number of cumulative SSPTBPs is the

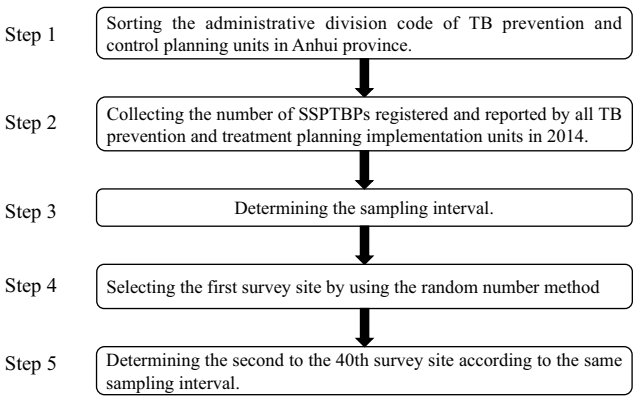

Figure 1 Specific steps for sampling.

first survey site. Step 5 is to determine the second to the 40th survey site (Figure 2) according to the same sampling interval. If the investigation site determined by random sampling cannot undertake the investigation due to special circumstances such as region, traffic or the number of patients, they can be replaced or supplemented downward in the prefecture-level cities under which the investigation sites belongs. In principle, the number of investigation sites replaced shall not exceed 5% of the total investigation sites.

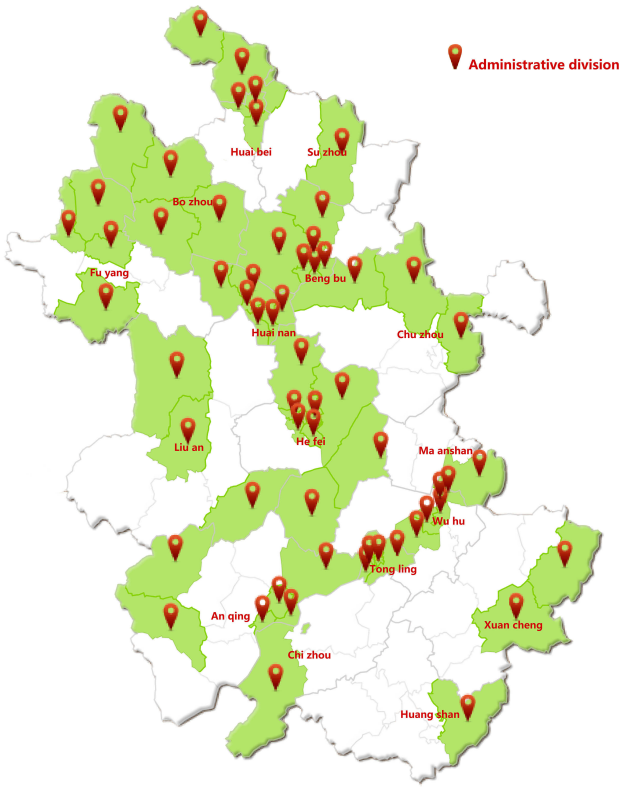

Figure 2 Layout of the county (district) administrative divisions covered by 40 survey sites.

Case Inclusion Principles

The following principles were followed in the inclusion of cases at each investigation site: 1) During the investigation, new cases and previously treated cases should be included in the survey consecutively from the beginning to the end according to the registration time, and they could be stopped after reaching the specified number of samples. 2) The investigated cases were newly registered cases from September 15, 2015to August 31, 2016. 3) There was no age range limited for the included cases. 4) TB clinic doctors register and classify the TB patients by asking their medical history. New cases refer to TB patients who have not received any anti-TB treatment course or who received anti-TB treatment course for less than one month. Previously treated cases include four groups of patients: relapse, return after loss to follow-up, treatment failure and re-treatment patients not included in the previous three groups. Re-treatment patients not included in the previous three groups refer to the chronic TB patients treated repeatedly. Recurrence refers to patients with a clear history of anti-TB treatment. After completing the prescribed chemotherapy course, the doctor believed that it had been cured. At this time, the sputum smear was positive or the lesion of the TB patient had obvious activity. Return refers to patients with TB who had been treated for more than one month and whose treatment had been interrupted for more than or equal to two months, and then continued to seek treatment in a medical institution because of clinical symptoms related to TB. Initial treatment failure refers to the smear sputum was positive at the 5th month of anti-TB treatment course. 4) No examination fee was charged for the included patients.

Case Information Collection and the Definition of Variables

Two trained clinicians obtained signed informed consent from eligible participants. Once informed consent was obtained, a survey questionnaire was administered and completed by each participant to collect sociodemographic data and clinical records about past anti-TB treatment courses. When the respondent was a child younger than 18 years old, the investigator explained the purpose and the content of the investigation to the participant and the legal guardian; the legal guardian signed the informed consent form. Sociodemographic data including sex, age, educational status, and family income in 2014 were collected. Clinical data including household contact with TB patients, past anti-TB treatment courses, the number of anti-TB treatment courses,

adverse drug reaction, duration of the first anti-TB treatment course, discontinuation of previous anti-TB treatment courses, and the number of discontinuation of previous anti-TB treatment courses were captured. After completing all the surveys at each survey site, investigators sealed all questionnaires and consent forms, and handed them to the survey coordinators.

One treatment course in "the number of anti-TB treatment courses" refers to one of the following conditions. First, including 6 months of treatment with the "2HRZE/4HR" (H, isoniazid, INH; R, rifampicin; Z, pyrazinamide; E, ethambutol, EMB) chemotherapy regimen, using "3HRZE/4HR" 6HRE chemotherapy regimen for 9 months, and the use of personalized treatment regimen. Second, within the same course of treatment, if the continuous treatment is stopped for no more than 2 months, it is considered as a course of treatment. Third, within the same course of treatment, the drug is discontinued for more than 2 months, and the treatment before the drug discontinuation is regarded as one treatment.

Bacteriological Examination

Three sputum specimens were obtained from each participant before starting TB treatment. Ziehl-Neelsen staining and smear microscopy for acid-fast bacilli was done on all specimens and the remainder of each specimen was stored at 4 degree Celsius. The best two specimens (highest smear positivity and if only one positive smear, the best smear-negative specimen) were selected for culture and the remainder of the smear-positive specimens stored at −20 degree Celsius. Positive specimens were cultured on lowenstein-jensen (LJ) medium with or without p-nitrobenzoic acid (PNB); growth of *Mycobacterium* TB (M. TB) was inhibited by PNB, while growth of non-TB *Mycobacterium* (NTM) was not affected. Positive cultures from each site were sent to provincial reference laboratories for DST.

DST was performed using the proportion method on LJ medium impregnated with INH, RIF, streptomycin (SM), EMB, ofloxacin (OFL) and kanamycin (KM). The concentrations of anti-TB drugs used were 0.2 μg/mL for INH, 40 μg/mL for RIF,2 μg/mL for EMB, 4 μg/mL for SM, 2 μg/mL for OFL, and 2 μg/mL for KM.[17] After completion of all DSTs 10% strains were randomly selected for retesting.

Any drug-resistant TB was defined as resistance to any of the anti-TB drugs among the six drugs (INH, RIF, EMB, SM, OFL or KM). Poly-resistance was defined as resistance to two or more drugs excluding INH and RIF. MDR was defined as resistance to INH and RIF and RR were defined as resistant to RIF. XDR was defined as resistance to at least INH, RIF, OFL, and KM.

Statistical Analysis

The input of the original data was performed by two members of the Tuberculosis Prevention and Treatment Institute of Anhui Province using Epidata software (version 3.1), respectively. Consistency test was carried out on the two databases, and the inconsistent data were determined by the two staff members after checking the original data. Odds ratio (OR) value and 95% confidence intervals (CIs) were used to evaluate the MDR-TB related univariate risk factors. All variables in the univariate analysis were used in the logistic regression analysis modeling for survey data. All relevant variables

Table 1 Drug Resistance to First-Line and Second-Line Anti-Tuberculosis Drugs in Anhui, China, 2015–2016

Resistance Profile	All SSPTBPs n=2530		New Cases n=2133		Previously Treated Cases n=397	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Any TB Drug Resistance						
Isoniazid	337	13.32(11.94–14.82)	223	10.45(9.13–11.92)	114	28.72(23.69–34.50)
Rifampin	289	11.42(10.14–12.82)	163	7.64(6.51–8.91)	126	31.74(26.44–37.79)
Streptomycin	321	12.69(11.34–14.15)	234	10.97(9.61–12.47)	87	21.91(17.55–27.03)
Ethambutol	74	2.93(2.30–3.67)	40	1.88(1.34–2.55)	34	8.56(5.93–11.97)
Ofloxacin	225	8.89(7.77–10.13)	139	6.52(5.48–7.69)	86	21.66(17.33–26.75)
Kanamycin	41	1.62(1.16–2.20)	30	1.41(0.95–2.00)	11	2.77(1.38–4.96)
Poly-resistance[a]	314	12.41(11.08–13.86)	191	8.96(7.73–10.32)	123	30.98(25.75–36.97)
MDR	193	7.63(6.59–8.66)	106	4.97(4.05–5.89)	87	21.91(17.83–26.00)
XDR	23	0.91(0.57–1.36)	13	0.61(0.32–1.04)	10	2.52(1.21–4.63)

Note: [a]Poly-resistance: resistance to two or more drugs excluding resistance to both isoniazid and rifampin.

Abbreviations: MDR, resistance to isoniazid and rifampin; XDR, resistance to at least isoniazid, rifampin, ofloxacin, and kanamycin; TB, tuberculosis; MDR, multidrug-resistant; XDR, extensively drug-resistant; SSPTBPs, sputum smear-positive tuberculosis patients.

Table 2 Analysis of Risk Factors for Multidrug-Resistant Tuberculosis (MDR-TB) in All Cases

Variables	All SSPTBPs				Univariate Analysis		Multivariate Analysis	
	Non-MDR	MDR	n	%	Odds Ratio (OR) (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Sex			2529			0.412		
Male	1813	144	1957	7.36	1			
Female	524	48	572	8.39	1.153(0.820–1.622)	0.412		
Age						0.138		
0~	70	7	77	9.09	1			
20~	570	42	612	6.86	0.726(0.314–1.679)	0.455		
40~	649	78	727	10.73	1.185(0.526–2.669)	0.683		
60~	1038	65	1103	5.89	0.611(0.270–1.384)	0.238		
Educational status						0.303		
Illiterate	671	42	713	5.89	1			
Primary school	590	49	639	7.67	1.327(0.866–2.033)	0.194		
Middle school	656	70	726	9.64	1.705(1.146–2.537)	0.009		
Senior high school	265	23	288	7.99	1.387(0.818–2.351)	0.225		
University	154	8	162	4.94	0.830(0.382–1.803)	0.638		
Family income in 2014						0.362		
<2500	254	19	273	6.96	1			
2500–4200	328	26	354	7.34	1.06(0.574–1.958)	0.853		
4201–20,000	729	66	795	8.30	1.210(0.712–2.056)	0.48		
20,001–50,000	630	60	690	8.70	1.271(0.744–2.173)	0.38		
>50,000	222	11	233	4.72	0.655(0.310–1.429)	0.665		
Household contact with TB patients						0.005		
No	2175	168	2343	7.17	1			
Yes	162	24	186	12.90	1.918(1.215–3.028)	0.005		
Past anti-TB treatment courses						<0.001		
No	2006	103	2109	4.88	1			
Yes	331	89	420	21.19	5.237(3.854–7.115)	<0.001		
The number of anti-TB treatment courses						<0.001		0.004
1	252	33	285	11.58	1		1	
2	42	24	66	36.36	4.071(2.202–7.528)	<0.001	5.367(1.258–22.897)	0.023
≥3	40	29	69	42.03	5.089(2.826–9.163)	<0.001	13.143(3.487–49.534)	0.001
Adverse drug reaction						0.573		
No	235	58	293	19.80	1			
Yes	98	28	126	22.22	1.179(0.713–1.949)	0.522		
Duration of the first anti-TB treatment courses						0.009		
6–8 months	163	40	203	19.70	1			
<6 months	140	28	168	16.67	0.822(0.487–1.388)	0.463		
>8 months	27	17	44	38.64	2.720(1.341–5.515)	0.006		
Discontinuation of previous anti-TB treatment courses						0.092		
No	197	42	239	17.57	1			
Yes	134	43	177	24.29	1.504(0.936–2.417)	0.091		

(*Continued*)

Table 2 (Continued).

Variables	All SSPTBPs				Univariate Analysis		Multivariate Analysis	
	Non-MDR	MDR	n	%	Odds Ratio (OR) (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Number of discontinuation of previous anti-TB treatment courses						0.008		
1	83	15	98	15.31	1			
2	19	9	28	32.14	2.429(0.935–6.308)	0.068		
≥3	32	19	51	37.25	3.238(1.489–7.040)	0.003		

were initially included in the model, and the forward method was used to select the final variables. The models were compared with the use of the maximum rescaled R^2 statistic. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (version 16.0).

Results

Case Inclusion

A total of 3047 cases were recruited in the 40 survey sites, including 2502 new cases and 545 previously treated cases. Of these, 2330 (76.5%) were males, while 717 (23.5%) were females. The average age of all cases is 53.59 ± 19.63 years, with a range between 8 years and 96 years old.

Results of DST

Of the 3047 SSPTBPs cases, DST was not done in 517 (16.97%): 275/517 had negative cultures, in 141 NTM was cultured and 101 cultures were contaminated. Finally, 2530 specimens were successfully cultured. DST results are showed in Table 1. The proportions of RR-TB were 11.42% (289/2530, 95% CI: 10.18–12.66%), 7.64% (163/2133, 95% CI: 6.38–8.62%) and 31.74% (126/397,95% CI: 27.38–36.60%), respectively, in all cases, new cases and previously treated cases, and the proportion of MDR-TB was 7.63% (193/2530, 95% CI: 6.59–8.66%), 4.97% (106/2133, 95% CI: 4.05–5.89%) and 21.91% (87/397,95% CI: 17.83–26.00%). The drug resistance rate of previously treated cases to OFL reached 21.66% (17.33–26.75%).

Analysis of Risk Factors for MDR-TB in All Cases

Of the 2530 cases with DST results, 2529 had completed questionnaires. Table 2 shows the analysis results of risk factors for MDR-TB in all SSPTBPs. The univariate analysis results showed that household contact with TB patients, past anti-TB treatment courses, the number of anti-TB treatment courses, duration of the first anti-TB treatment courses, and number of interruptions to past anti-TB treatment courses were related to MDR-TB ($P<0.05$), while the other factors such as sex, age, educational status, household income in 2014, adverse drug reaction, and past anti-TB treatment interruption had no significant association with MDR-TB ($P>0.05$). Results of multivariate analysis showed only the number of anti-TB treatment courses was included in the model ($P=0.004$), and cases who received two or more anti-TB treatment courses had a significantly increased risk for developing MDR-TB compared with those who received one anti-TB treatment courses, respectively (OR=5.367, 95% CI=1.258–22.897, $P<0.001$; OR=13.143, 95% CI=3.487–49.534, $P<0.001$).

Analysis of Risk Factors for MDR-TB in New Cases

Among the 2529 SSPTBPs with questionnaire, 2132 patients were new cases. Table 3 shows the analysis results of risk factors for MDR-TB in new cases. Univariate analysis did not find that age, sex and other factors were related to the generation of MDR-TB.

Analysis of Risk Factors for MDR-TB in Previously Treated Cases

A total of 397 valid questionnaires for previously treated cases of SSPTBPs were collected, and Table 4 shows the analysis results of risk factors for MDR-TB. Univariate analysis showed that age, the number of anti-TB treatment courses, duration of the first anti-TB treatment courses, discontinuation of previous anti-TB treatment courses, and number of discontinuation of previous anti-TB treatment courses were significantly associated with MDR-TB

Table 3 Analysis of Risk Factors for Multidrug-Resistant Tuberculosis (MDR-TB) in New Cases

Variables	New Cases				Univariate Analysis	
	Non-MDR	MDR	n	%	Odds Ratio (OR) (95% CI)	p-value
Sex						0.58
Male	1550	77	1627	4.73	1	
Female	478	27	505	5.35	1.137(0.725–1.784)	0.576
Age						0.126
0~	69	7	76	9.21	1	
20~	527	27	554	4.87	0.505(0.212–1.203)	0.123
40~	543	34	577	5.89	0.617(0.263–1.446)	0.267
60~	888	36	924	3.90	0.4(0.172–0.931)	0.034
Educational status						0.181
Illiterate	581	23	604	3.81	1	
Primary school	496	21	517	4.06	1.070(0.585–1.956)	0.827
Middle school	570	40	610	6.56	1.773(1.048–2.999)	0.033
Senior high school	237	14	251	5.58	1.492(0.755–2.949)	0.25
University	143	6	149	4.03	1.060(0.424–2.651)	0.901
Family income in 2014						0.692
<2500	210	11	221	4.98	1	
2500–4200	283	19	302	6.29	1.282(0.597–2.751)	0.524
4201–20,000	633	32	665	4.81	0.965(0.478–1.949)	0.921
20,001–50,000	554	30	584	5.14	1.034(0.509–2.100)	0.927
>50,000	197	7	204	3.43	0.678(0.258–1.785)	0.432
Household contact with TB patients						0.41
No	1896	95	1991	4.77	1	
Yes	132	9	141	6.38	1.361(0.672–2.757)	0.392

(P<0.05). Factors such as sex, educational status and household income in 2014 were not related to MDR-TB. When all the above single variable was included in the logistic regression model, only the number of anti-TB treatment courses was included in the model (P=0.002). Subgroup analysis results show cases who received two or more anti-TB treatment courses had a significant association with MDR-TB compared with those who received one anti-TB treatment courses (OR=4.544, 95% CI=1.054–19.590, P=0.042; OR=11.100, 95% CI=2.913–42.300, P< 0.001).

Discussion

In this study, the proportion of RR in SSPTBPs in Anhui Province was systematically sampled for the first time. Our results showed that the proportion of RR in new cases and previously treated cases was 7.64% (6.38–8.62%) and 31.74% (27.38–36.60%), respectively, which was higher than the national average of 7.1% (5.6–8.7%) and 24% (20–28%), and also above the global average of 4.1% (2.8–5.3%) and 19% (9.8–27%).[18] The reasons for the high RR-TB prevalence in this study are not clear and further studies to determine possible reasons are needed. As in other studies, previously treated patients have a higher rate of RR-TB, but even new TB cases had a high rate of RR-TB.[19] The reasons for this need to be explored.

Based on the prevalence of MDR-TB from this survey, we estimated that there are approximately 727 MDR-TB patients in Anhui Province in 2017: 451 patients were new cases, accounting for 62%, and 276 patients were previously treated cases, accounting for 38% (The estimation formula: M=Pn×Cn+Pr×Cr, M: total number of MDR-TB patients, Pn: the proportion of MDR-TB in new cases, which equals to 4.97% in this study, Pr: the proportion of MDR-TB in previously treated cases of SSPTBPs, which equals to 21.91%, Cn: the number of new cases in Anhui Province in 2017, which equals to 9071, Cr: the number of previously treated cases in Anhui Province in 2017, which equals to 1259.). However, only 310 MDR-TB patients were actually registered in Anhui Province in 2017, including 107 new cases, accounting for 34.5%, and

Table 4 Analysis of Risk Factors for Multidrug-Resistant Tuberculosis (MDR-TB) in Previously Treated Cases

Variables	Previously Treated Cases				Univariate Analysis		Multivariate Analysis	
	Non-MDR	MDR	n	%	Odds ratio (OR) (95% CI)	p-value	Adjusted OR Values	Adjusted p-value
Sex						0.056		
Male	263	67	330	20.30	1			
Female	46	21	67	31.34	1.785(0.998–3.194)	0.051		
Age						0.008		
20~	43	15	58	25.86	1			
40~	106	44	150	29.33	1.190(0.600–2.360)	0.619		
60~	160	29	189	15.43	0.523(0.257–1.062)	0.073		
Educational status						0.595		
Illiterate	90	19	109	17.43	1			
Primary school	94	28	122	22.95	1.395(0.728–2.675)	0.316		
Middle school	86	30	116	25.86	1.634(0.856–3.119)	0.137		
Senior high school	28	9	37	24.32	1.506(0.612–3.702)	0.373		
University	11	2	13	15.38	0.852(0.174–4.160)	0.843		
Family income in 2014						0.077		
<2500	44	8	52	15.38	1			
2500–4200	45	7	52	13.46	0.856(0.286–2.560)	0.78		
4201–20,000	95	34	130	26.15	1.968(0.842–4.601)	0.118		
20,001–50,000	77	30	107	28.30	2.143(0.904–5.081)	0.084		
>50,000	24	4	28	14.29	0.917(0.250–3.361)	0.896		
Household contact with TB patients						0.071		
No	278	73	351	20.80	1			
Yes	30	15	45	33.33	1.890(0.966–3.699)	0.141		
Past anti-TB treatment courses								
No	0	0	0					
Yes	303	88	391	22.51				
The number of anti-TB treatment courses						<0.001		0.002
1	221	33	254	12.99	1		1	
2	42	24	66	36.36	3.827(2.057–7.119)	<0.001	4.544(1.054–19.590)	0.042
≥3	40	29	69	42.03	4.855(2.660–8.864)	<0.001	11.100(2.913–42.300)	<0.001
Adverse drug reaction						0.584		
No	213	58	271	21.40	1			
Yes	89	28	117	23.93	1.155(0.691–1.933)	0.582		
Duration of the first anti-TB treatment courses						0.023		
6–8 months	160	40	200	20	1			
<6 months	115	28	143	19.58	0.889(0.517–1.527)	0.669		
>8 months	25	17	42	40.48	2.482(1.222–5.041)	0.012		
Discontinuation of previous anti-TB treatment courses						0.038		
No	187	42	229	18.34	1			
Yes	114	43	157	27.39	1.665(1.026–2.703)	0.039		

(*Continued*)

Table 4 (Continued).

Variables	Previously Treated Cases				Univariate Analysis		Multivariate Analysis	
	Non-MDR	MDR	n	%	Odds ratio (OR) (95% CI)	p-value	Adjusted OR Values	Adjusted p-value
Number of discontinuation of previous anti-TB treatment courses						0.053		
1	67	15	82	18.29	1			
2	20	9	29	31.03	2.010(0.765–5.279)	0.156		
≥3	33	19	52	36.54	2.572(1.161–5.695)	0.02		

203 previously treated cases, accounting for 64.5%. This result suggested new and previously treated TB patients should have DST done so that an appropriate anti-TB treatment regimen can be started in all patients.

This study found that the drug resistance rate of previously treated patients to ofloxacin reached 21.66% (17.33–26.75%), much higher than the average level of 8.7% (6.1–11.2%) in China[3] and 17% in Dalian city,[7] and close to the WHO-reported rate of resistance to fluoroquinolones (FQs) in global MDR-TB patients (22%).[1] High drug resistance of ofloxacin may be related to a number of factors. In China, FQs drugs are the preferred drug for undiagnosed respiratory bacterial infections,[20] and readily available on the market. What's more, excessive and premature use of ofloxacin in the anti-TB diagnostic treatment is also one of the reasons. FQs have been recommended as first-line drugs for the treatment of MDR-TB due to their high activity against *M.tuberculosis*. Unfortunately, poorly controlled use of FQs leads to the emergence of FQs resistance in *M.tuberculosis*, which might influence the therapeutic effect for MDR-TB patients.[21] Thus, it is significant for us to accept that strict control of the use of FQs is important for the treatment of MDR-TB.

There are still several limitations in this study. First, the cases included in this survey are all SSPTBPs in the outpatient clinic of TB, rather than all TB patients in the population. Therefore, there are certain restrictions when the drug resistance results are extrapolated to all TB patients. Second, the factors affecting the production of MDR-TB are complex. Because the focus of this survey is to understand the prevalence of MDR-TB in Anhui Province, in order to ensure the feasibility of the survey, the influencing factors included in the questionnaire are not comprehensive enough. Foreign research mentioned HIV infection, drug use, and the economic burden and psychological factors of patients are not included in this survey. We will further discuss these factors and MDR-TB in the subsequent study.

Conclusion

The prevalence of MDR-TB was high among the SSPTBPs in Anhui Province, and past anti-TB treatment courses were associated with MDR-TB.

Abbreviations

CIs, Confidence intervals; EMB, Ethambutol; INH, Isoniazid; KM, Kanamycin; LJ, Lowenstein-jensen; MDR-TB, multidrug-resistant tuberculosis; MTB, *Mycobacterium tuberculosis*; NTM, Non-*Mycobacterium tuberculosis*; OFL, Ofloxacin; OR, Odds ratio; PNB, P-nitrobenzoic acid; RIF, Rifampin; RR-TB, Rifampin resistant tuberculosis; SM, Streptomycin; SSPTBPs, Sputum smear positive TB patients; WHO, World Health Organization.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request, and some of the data cannot be accessed due to patient confidentiality.

Ethics and Consent Statement

This protocol was approved by the Ethics Committee of Tuberculosis Prevention and Treatment Institute of Anhui Province (Anhui Chest Hospital) (Approval number: AHJF-IRB-SC-20150506). We confirmed that our study was conducted in accordance with the Declaration of Helsinki. All included patients signed the written informed consent form indicating their consent to participate in this survey. When the respondent is a child younger than 18 years old, the investigator explained the purpose and the content of the investigation to the respondent and its

guardians face to face, and the guardians signed the written informed consent form after thorough consideration.

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Disclosure

The authors declare that they have no competing interests in this work.

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