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Trends and Characteristics of Drug-resistant Tuberculosis in Rural Shandong, China

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Highlights:

- The increasing prevalence of MDR TB has led to new challenges.
- Studying of DR TB and MDR TB in rural areas is vital to TB control in China.
- Increasing MDR TB especially primary MDR TB characterize DR TB cases in rural China.

Abstract

Objectives: We aim to describe the secular trends for drug-resistant tuberculosis (DR TB) and to identify unique characteristics of multidrug-resistant TB (MDR TB) in rural China.

Methods: A retrospective study of TB data collected from 36 tuberculosis prevention and control institutions serving rural populations in Shandong Province, China, from 2006 to 2015 was conducted.

Results: Approximately 8.3% of patients suffered from MDR, among which 70% were new treated patients, and this rate has increased at a yearly rate of 1.3% during the last decade. An increase in the percentage of overall first-line drug resistance against isoniazid (INH), rifampin (RFP), ethambutol (EMB), and streptomycin (SM) was confirmed (P<0.05). The percentage of MDR TB in new and previously treated cases increased at yearly rates of 9.9% and 11.1%, respectively. MDR TB patients were more likely to be female (OR, 1.58; 95% CI, 1.32-1.89),
smoking (OR, 1.75; 95% CI, 1.47-2.07), having recent TB contact (OR, 1.58; 95% CI, 1.04-2.42), and retreated (OR, 2.89; 95% CI, 2.46-3.41).

**Conclusions:** Increasing MDR TB and rates of primary MDR TB characterize DR TB cases in rural China. Persistent efforts need to be made among MDR TB patients in future TB control strategies.

**Keywords:** multidrug-resistant tuberculosis; primary transmission; rural; epidemiology

**Introduction**

Microbial drug resistance has become a major public health concern worldwide [1]. Due to persistent international efforts to combat tuberculosis (TB), both the global mortality rate and incidence rate have decreased over the past two decades [2]. However, the increasing prevalence of drug-resistant tuberculosis (DR TB) has led to new challenges [3]. As an expanding threat, it is estimated that MDR TB, defined as resistance to isoniazid (INH) and rifampin (RFP), has grown to 480,000 new cases (2015 cohort) with 210,000 deaths/year (2013 cohort) [2]. With catastrophic cost, poor adherence, prolonged treatment duration and inadequate effective drugs, MDR TB has been associated with worse treatment outcomes than drug-susceptible TB [4-7]. The serious epidemic of MDR TB places patients just one step away from having extensively
drug-resistant (XDR) and also increases the rate of treatment failure and causes enormous social and economic disruption [8].

China has the second highest number of TB cases and accounts for 25% of the MDR TB population in the world [9]. As China has the largest agricultural population in the world, approximately 64.9% of TB patients and 80% of MDR TB patients in China live in rural areas [10-11]. Due to poor regional socioeconomic status (living conditions, health and nutritional status, money to pay for health care and access to health services) [12], more and more patients have delayed or received inappropriate treatments, which have consequently increased the prevalence and mortality rate of TB in poor rural areas compared with economically developed urban areas [13]. With economic development and urbanization, an increasing population, up to 211 million in 2010, migrated from rural to urban areas in China, leading to the spreading of TB nationwide [14]. Thus, studying of DR TB specifically MDR TB in rural areas is of key importance for monitoring and controlling TB in China. Previous studies on TB in rural areas were limited by the short time span and small sample size of culture-positive TB in China [15-16].

Shandong is a province located on the east coast of China with a population of 95 million and a rural population of 57 million according to the *Sixth National Census*. An estimated 211,900 people in Shandong were infected with TB with 66.7% of the cases being rural residents
according to the *Fifth National TB Epidemiological Survey* in Shandong province [11]. The purpose of the present study was to summarize the changes between different drug-resistant patterns over time on the basis of drug susceptibility testing (DST) for first-line drugs among the rural population in Shandong Province, China, in the last decade, to provide effective intervention strategies for the prevention and control of DR TB in similar populations.

**Materials and Methods**

**Study population and data collection**

We collected information from consecutive culture-confirmed TB cases among the rural population in Shandong Province from the China Information System for Disease Control and Prevention (CISDCP) from 2006 to 2015. Two province-level hospitals, Shandong Provincial Hospital and Shandong Provincial Chest Hospital (SPCH), and 21 county-level and 13 municipal-level local health departments in Shandong Province constituted the 36 monitoring sites in this retrospective study. Monitoring sites were selected based on convenience and to reflect a range of TB burdens and clinical capacity. In 2004, the Center for TB Control and Prevention of Shandong province, including SPCH, set up the provincial health department Katharine Hsu International Research Center of Human Infectious Diseases (KICID), where the patients’ information was collected and recorded by trained
researchers on standard case report forms. KICID has been responsible for laboratory quality assurance and TB surveillance in Shandong province since its inception.

*Mycobacterium tuberculosis* was identified by culturing and susceptibility to INH, RFP, ethambutol (EMB), and streptomycin (SM) was identified by using DST. Sociodemographic data for all of the patients including age, sex, smoking history, excess alcohol consumption, TB contact history and prior TB treatment history were collected and recorded.

**Laboratory Methods**

All samples available were processed for smear and culture. Tissue samples were also examined for the presence of granulomas. By using Ziehl-Neelsen staining, the presence of acid-fast bacilli (AFB) was confirmed. Culturing was performed on Lowenstein-Jensen (LJ) culture medium. After thorough assessment of all the evidence derived from growth characteristics, morphologic characteristics of the colony, and the result for inhibition by P-nitrobenzoic acid, *M. tuberculosis* was selected [9]. Furthermore, the samples containing non-tuberculosis mycobacteria (NTM) were rejected.

Acid buffer LJ medium DST was performed using the proportion method with the following antibiotic concentrations: (1) INH (0.2 μg/mL), (2) RFP (40 μg/mL), (3) EMB (2.0 μg/mL), and (4) SM (4.0 μg/mL).
Resistance was defined as more than 1% growth for any anti-TB drug.

**Laboratory Quality Control**

External quality assessment (EQA) for smear, culture and DST in county and district level laboratories was conducted by the prefectural and provincial TB laboratories, accordingly, EQA in the provincial reference laboratories and the National Tuberculosis Reference Laboratory (NTRL) was conducted by the Supranational Tuberculosis Reference Laboratory (STRL) based on the WHO guideline [17]. Blinded re-testing of a random selection of approximately 10% of the isolates from each laboratory by a superior laboratory was essential.

**Data inclusion and definitions**

All of the TB cases in rural areas that had a positive *M. tuberculosis* culture with DST results and demographic and clinical information were included. TB patients with non-tuberculous mycobacteria (NTM) as well as HIV (in China HIV-positive patients are immediately transferred to an HIV-specialized hospital) were excluded.

Drug-susceptible TB was defined as TB isolates susceptible to all the four tested first-line drugs. MDR TB was defined as TB resistant to at least INH and RFP. A “new case” is defined as a patient who had never been treated for TB or had taken <1 month of anti-TB drugs in the past; A “previously treated case” is defined as a patient who had received ≥1 month of anti-TB drugs in the past [17].
**Statistical analysis**

The changes in the proportions of different resistance patterns over time were confirmed using the Chi-Square test for trends and linear regression. Pearson’s $X^2$ test was used to compare categorical variables for univariable analysis. Multivariable logistic regression analysis was used to identify unique characteristics of MDR TB. The odds ratios (OR), 95% confidence interval (CI) and P value for individual variables were obtained using a logistic regression model, and $P<0.05$ was considered to be statistically significant. We used SPSS software version 17.0 for the statistical analysis.

**Results**

**Case Estimates**

A total of 10,977 cases were identified with *M. tuberculosis* in rural Shandong during the last decade. First, we excluded 1198 (10.9%) patients without DST result and 35 (0.3%) patients without demographic or clinical information. Then, we excluded 171 (1.6%) patients with NTM. Finally, sum to 9,573 (87.2%) cases were included. The average age of these patients was 51.0 (mean±SD, 51.0±19.3) years old and 79.1% were male.

**Drug Resistance Patterns**

Among the 9,573 TB cases, the resistance rate for SM was 17.7%, followed by INH (16.5%), RFP (10.0%), and EMB (4.4%). The
prevalence of MDR was 794 (8.3%), while another 951 (9.9%) patients had resistance to either INH or RFP (but not both). A total of 2,037 (24.1%) cases were resistant to at least one first-line drug and 289 (3.0%) cases were resistant to all the four tested first-line drugs.

MDR TB was confirmed in 6.8% of new cases and 17.1% of previously treated cases. Another 9.2% and 14.3% of new and previously treated TB cases, respectively, were resistant to either INH or RFP (but not both). An estimated 21.8% and 37.1% of new and previously treated TB cases, respectively, were resistant to at least one of the four first-line anti-tuberculosis drugs (Table 1).

**Trends Overtime**

Among the included patients (9573 cases), it is noteworthy that the percentage of drug-susceptible TB decreased from 78.6% in 2006 to 71.9% in 2015, decreasing at a yearly rate of 1.0% ($R^2=0.5611$; Chi-square test for trends: $X^2=29.242$, $P<0.001$). In contrast, the percentage of overall first-line drug resistance for INH, RFP, EMB and SM, and MDR TB increased significantly ($P<0.001$) over the past decade ($X^2=22.831$ for INH resistance, increasing at a yearly rate of 4.8% ($R^2=0.47$) from 12.6% to 19.2%; $X^2=62.297$ for RFP resistance, increasing at a yearly rate of 8.2% ($R^2=0.69$) from 6.4% to 13.1%; $X^2=38.933$ for EMB resistance, increasing at a yearly rate of 18.0% ($R^2=0.68$) from 1.5% to 6.6%; $X^2=36.392$ for SM resistance, increasing at
a yearly rate of 5.1% (R²=0.74) from 14.7% to 22.9%; and X²=43.629 for MDR TB, increasing at a yearly rate of 9.4% (R²=0.53) from 4.9% to 11.1%) (Figure 1 and Figure 2). Moreover, mono-resistance analysis showed a statistically significant increase in the RFP mono-resistance (RMR) proportion (X²=9.017, P=0.003), though INH, EMB, and SM mono-resistance showed no statistically significant changes during the last decade.

To better understand the epidemic trends in TB cases with different treatment histories, a further breakdown of new and previously treated TB cases was conducted. This breakdown estimated that there was an increasing yearly rate of 9.9% (R²=0.53) for new treated MDR TB and 11.1% (R²=0.71) for previously treated MDR TB cases during the last decade; these changes were statistically significant (P<0.001) using the Chi-square test for trends (X²=51.279 and 60.481, respectively) (Figure 2). The percentage of new treated MDR TB among MDR TB patients increased from 67.5% in 2006 to 76.0% in 2015, increasing at a yearly rate of 1.3% (R²=0.38; Chi-square test for trends: X²=12.291, P<0.001) (Figure 3). We also analyzed trends for other drug resistance patterns in new and previously treated TB cases. We found that the overall drug resistance rate was increasing significantly at a yearly rate of 4.9% (R²=0.40), 8.8% (R²=0.56), 18.0% (R²=0.65), and 5.2% (R²=0.67) for INH, RFP, EMB, and SM, respectively, in new TB cases during our study.
period (Chi-square test for trends: $X^2=19.699$, $P<0.001$; $X^2=53.892$, $P<0.001$; $X^2=36.196$, $P<0.001$; and $X^2=35.933$, $P<0.001$, respectively). Coincidentally, in previously treated TB cases, the overall drug resistance rate increased significantly at a yearly rate of 6.6% ($R^2=0.69$), 10.0% ($R^2=0.76$), 19.7% ($R^2=0.44$), and 5.4% ($R^2=0.53$) for INH, RFP, EMB, SM, respectively, during our study period (Chi-square test for trends: $X^2=14.805$, $P<0.001$; $X^2=30.753$, $P<0.001$; $X^2=9.112$, $P=0.003$; and $X^2=10.369$, $P=0.001$, respectively). The mono-resistance analysis showed an increasing yearly rate of 9.3% ($R^2=0.55$) for new treated RMR TB and 14.0% ($R^2=0.45$) for previously treated RMR TB cases; these changes were statistically significant using the Chi-square test for trends ($X^2=4.506$, $P=0.034$; and $X^2=8.222$, $P=0.004$, respectively). In contrast, INH mono-resistance in previously treated TB cases and EMB and SM mono-resistance in both new and previously treated TB cases showed no statistically significant changes. The percentage of INH mono-resistance in new TB cases decreased significantly from 4.4% to 2.2%, decreasing at a yearly rate of 7.4% ($R^2=0.30$; Chi-square test for trends: $X^2=6.261$, $P=0.012$).

**Demographic and Clinical Characteristics**

Table 2 shows the characteristics of patients with or without MDR TB in detail. Univariable comparison showed that the following characteristics were associated with the presence of MDR TB: (1) female,
(2) smoking, (3) recent TB contact and (4) TB treatment history. Patients aged 15-24 years were less likely to have MDR TB. On the basis of the variables included in the univariable comparison, the final multiple logistic regression model predicted MDR TB based on the following characteristics: (1) female (OR, 1.58; 95% CI, 1.32-1.89), (2) smoking (OR, 1.75; 95% CI, 1.47-2.07), (3) recent TB contact (OR, 1.58; 95% CI, 1.04-2.42) and (4) TB treatment history (OR, 2.89; 95% CI 2.46-3.41).

Discussion

This retrospective study attempted to systematically investigate the secular trends of DR TB and to identify characteristics of MDR in *M. tuberculosis* strains from TB patients in rural settings in Shandong, the second largest province located on the eastern coast of China. To our knowledge, this is one of the largest retrospective study from the aspect of both time span and sample size for culture-positive TB that describes the epidemiology of DR TB among rural populations in Shandong, China over the past decade.

In 2009, the Chinese government established the rural New Cooperative Medical Scheme (NCMS), a health insurance scheme for rural patients, and devised a plan for MDR TB prevention and control [18-19]. Although these efforts appear to be helpful, with low reimbursement rates for in-patients and no reimbursement rates for out-patients, this strategy may not be sufficient for TB treatment and
control in rural China and may run into bottlenecks. In this study, the percentage of drug susceptible TB in new and previously treated cases and INH mono-resistance TB in new cases decreased during the last decade. In contrast, an increase in the percentage of overall first-line drug resistance for INH, RFP, EMB and SM, RMR and MDR TB with new and previously treated cases in rural areas during the last decade was confirmed.

During the study periods, the percentage of new treated MDR TB among MDR TB patients increased from 67.5% in 2006 to 76.0% in 2015, increasing at a yearly rate of 1.3%. This indicates ongoing primary transmission of MDR TB strains in rural China. Consistent with previous surveys, patients who had a recent TB contact history were more likely to have MDR TB [20-21]. To make matters worse, the percentage of recent TB contact as a sensitive indicator for primary transmission was greatly underestimated due to a lack of diagnosis and unawareness of the disease for those infected as well as disguising of TB status for the susceptible population [22]. Delays (patient, provider, diagnostic, and treatment delays) for suspected TB patients affected the percentage of infection among close contacts and contributed to the emergence of drug resistance, particularly for MDR [23-24]. This phenomenon may be even more serious in rural areas, which harbor a higher burden of TB/MDR TB and have much poorer living conditions, poorer health and nutritional status,
less money to pay for health care, insufficient laboratory facilities, and fewer qualified health professionals [12, 25]. Up to 70% of the patients with MDR TB had diseases that were resistant to at least INH and RFP before they received standard first-line short-course treatment in this study. With poor and even no standard TB infection control (IC) measures in some undeveloped regions in China, the primary spread of M. tuberculosis within the general population and cross-infection between TB patients particularly in health-care facilities are quite serious [26]. Continuous efforts are urgently needed to control the on-going primary transmission of MDR TB in rural China.

Shandong province has implemented directly observed treatment strategy (DOTS) therapy since 1992, the strategy has universally covered TB patients at the county level since 1995, the cure rate of active TB cases by DOTS reached over 90% at the county level according to mid-evaluation on carrying out “TB control planning of China (2001-2010)” in Shandong Province [27]. However, the prevalence and continual rise of DR TB and MDR TB stands to derail the implementation and completion of DOTS in rural China [28]. During the study period, MDR TB with prior anti-TB treatment history which may occurred by acquisition, re-infection or re-current increased from 8.4% in 2006 to 21.8% in 2015, increasing at a yearly rate of 11.1%. The widespread and inappropriate use of anti-TB drugs might enable the
selection of drug-resistant strains, which also accelerated the occurrence of acquired MDR [9, 29-30]. A previous study demonstrated that INH or RMR was an independent predictor for acquired MDR TB [9]. An increase in the overall resistance rate to INH, RFP, and RMR was confirmed in this study. An estimated 9.2% of new and 14.3% of previously treated TB patients had resistance to either INH or RFP (but not both), placing them just one step away from having MDR TB. The government provided “free” TB treatment for all TB patients covering only some diagnostic tests and first-line anti-mycobacterial medications, however catastrophic second-line anti-mycobacterial medications and “out of pocket” expenditures, such as transport, additional food, symptom-relieving medicines, or indirect expenses associated with lost income, lead to more and more patients, especially those living in poor rural areas, dropping out of and/or discontinuing treatment even under DOTS [31-33]. These inadequate (poor regimens) treatment, irregular (poor compliance) and incomplete (defaulting) treatments can exacerbate treatment failure and increase the risk of MDR TB [5-7]. The already serious situation of DR TB in China could easily be much worse if increasing populations migrated from rural to urban areas [34]. Thus, controlling MDR in rural areas may be one of the most significant factors in future TB control strategies.

Similar to previous studies, we identified several characteristics of
MDR TB among rural TB cases. In this study, special attention should be paid to TB patients who are female [35-36], smokers [37-38], previously treated [20, 35] and in contact with other TB patients [20-21].

This is the first study devoted to assessing the changes in different DR TB patterns from a retrospective perspective and identifying unique MDR TB case characteristics in rural China. The results imply that the DR TB situation in China could easily deteriorate if MDR TB and primary transmission of MDR strains increase in rural areas.

This study did have some limitations. First, because only one province on the eastern coast of China was examined, the economic and regional disparities limited the generalizability of the results. Second, according to the National Survey of Drug-Resistant TB in 2007, one third of patients with MDR TB were resistant to either ofloxacin or kanamycin [9], placing them one step away from XDR TB. However, the lack of DST for second-line drugs impeded us from further understanding the extent of drug-resistant, extremely DR and totally DR TB that were associated with treatment outcomes much worse than MDR TB [39-41]. Third, because all of the patients were culture-confirmed HIV-seronegative TB cases with little information on their education, incomes, and living conditions accessible from the medical records, we failed to show the relationships between these factors and the DR TB epidemic. Finally, the lack of genotyping, a gold standard for identifying the origin of resistant isolates,
impeded us from correlating the mutations in the prevalent strains with observed resistance in this region of study with observations in other parts of China and the world.

In conclusion, we demonstrated an increase in MDR TB in rural China over the last decade. MDR TB strains are mainly transmitted by airborne infection in rural China. Effective TB IC strategies are urgently needed to control the on-going primary transmission of MDR TB, especially among people grouped closely with diagnosed TB patients. DST for both first- and second-line anti-TB drugs is essential for more individualized anti-TB regimens. Additionally, on-going reforms for financing DOTS (TB diagnosis and treatment) in rural areas will be essential components of effective interventions for TB prevention and control in China.

**Acknowledgements**

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**Ethical clearance**

This study was approved by the Ethics Committee of Shandong Provincial Hospital, which is affiliated to Shandong University. Patient
Records were anonymized and de-identified before analysis.

Conflict of interest

None.
References


7. Yang BF, Biao XU, Jiang WL, Zhou PY. Study on the epidemiology and determinants of drug-resistant tuberculosis in northern rural area of


Figure legends

Figure 1. Drug-resistance pattern trends among 9,573 culture-confirmed TB cases in rural China from 2006 to 2015.

For INH resistance ($X^2=22.831$, $P<0.001$; linear regression formula: $R^2=0.47$, x-coefficient=0.006, SE=0.130); for RFP resistance ($X^2=62.297$, $P<0.001$; linear regression formula: $R^2=0.69$, x-coefficient=0.008, SE=0.051); for EMB resistance ($X^2=38.933$, $P<0.001$; linear regression formula: $R^2=0.68$, x-coefficient=0.005, SE=0.017); and for SM resistance ($X^2=36.392$, $P<0.001$; linear regression formula: $R^2=0.74$, x-coefficient=0.008, SE=0.131).

EMB=ethambutol, INH=isoniazid, RFP=rifampin, SE=standard error, SM=streptomycin, and TB=tuberculosis.

Figure 2. Trends for MDR TB in rural China from 2006 to 2015.

For MDR ($X^2=43.629$, $P<0.001$; linear regression formula: $R^2=0.53$, x-coefficient=0.006, SE=0.043); for MDR among new treated patients ($X^2=51.279$, $P<0.001$; linear regression formula: $R^2=0.53$, x-coefficient=0.007, SE=0.027); and for MDR among previously treated patients ($X^2=60.481$, $P<0.001$; linear regression formula: $R^2=0.71$, x-coefficient=0.015, SE=0.094).

MDR-TB=multidrug-resistant tuberculosis and SE=standard error.

Figure 3. Trends for the new treated MDR TB proportion among MDR TB cases in rural China from 2006 to 2015.
($X^2 = 12.291, \ P < 0.001$; linear regression formula: $R^2 = 0.38$, x-coefficient=0.027, SE=0.511).

MDR TB=multidrug-resistant tuberculosis and SE=standard error.

Figure 1
Figure 2
Figure 3
Table 1 Drug resistance to first-line drugs among new and previously treated patients in rural areas of Shandong, China from 2006-2015

<table>
<thead>
<tr>
<th>Drug resistance</th>
<th>New treated patients (n=8155)</th>
<th>Previously treated patients (n=1418)</th>
<th>Total (n=9573)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Any resistance to first-line drug</td>
<td>1781 (825)</td>
<td>21.8 (10.1)</td>
<td>526 (182)</td>
</tr>
<tr>
<td>INH</td>
<td>1196 (282)</td>
<td>14.7 (3.5)</td>
<td>386 (69)</td>
</tr>
<tr>
<td>RFP</td>
<td>657 (64)</td>
<td>8.1 (0.8)</td>
<td>300 (31)</td>
</tr>
<tr>
<td>EMB</td>
<td>315 (24)</td>
<td>3.9 (0.3)</td>
<td>105 (5)</td>
</tr>
<tr>
<td>SM</td>
<td>1317 (455)</td>
<td>16.2 (5.6)</td>
<td>377 (77)</td>
</tr>
<tr>
<td>Resistance to 2 drugs</td>
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<tr>
<td>INH+RFP</td>
<td>62</td>
<td>0.8</td>
<td>37</td>
</tr>
<tr>
<td>INH+SM</td>
<td>305</td>
<td>3.7</td>
<td>62</td>
</tr>
</tbody>
</table>
| Combination         | Cases | Rate | New | Loss | Total | Multi
|---------------------|-------|------|-----|------|-------|-------
| RFP+SM              | 31    | 0.4  | 23  | 1.6  | 54    | 0.6   |
| Resistance to 3 drugs |       |      |     |      |       |       |
| INH+RFP+EMB         | 11    | 0.1  | 6   | 0.4  | 17    | 0.2   |
| INH+RFP+SM          | 267   | 3.3  | 122 | 8.6  | 389   | 4.1   |
| INH+EMB+SM          | 39    | 0.5  | 13  | 0.9  | 52    | 0.5   |
| RFP+EMB+SM          | 7     | 0.1  | 3   | 0.2  | 10    | 0.1   |
| At least INH/RFP    | 749   | 9.2  | 202 | 14.3 | 951   | 9.9   |
| MDR, overall        | 552   | 6.8  | 242 | 17.1 | 794   | 8.3   |
| Resistance to 4 drugs | 212   | 2.6  | 77  | 5.4  | 289   | 3.0   |

EMB, ethambutol; INH, isoniazid; MDR, multidrug-resistant; RFP, rifampin; SM, streptomycin.

Numbers and rates of mono-first-line drug resistant cases are shown in parentheses.
Table 2 Univariable and multivariable logistic regression analyses of unique characteristics for MDR-TB among TB cases in rural China from 2006 to 2015

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-MDR TB (n=8779)</th>
<th>MDR-TB TB (n=794)</th>
<th>Univariable OR (95%CI)</th>
<th>P value</th>
<th>Multivariable OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
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<tr>
<td>0-14</td>
<td>63 (0.7)</td>
<td>3 (0.4)</td>
<td>0.53</td>
<td>0.27</td>
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<td></td>
<td>(0.16-1.68)</td>
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<tr>
<td>15-24</td>
<td>1198</td>
<td>86</td>
<td>0.77</td>
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<tr>
<td></td>
<td>(13.6)</td>
<td>(10.8)</td>
<td>(0.61-0.97)</td>
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<tr>
<td>25-44</td>
<td>1818</td>
<td>174</td>
<td>1.08</td>
<td>0.42</td>
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<tr>
<td>Age</td>
<td>Cases</td>
<td>Controls</td>
<td>OR</td>
<td>95% CI</td>
<td></td>
<td></td>
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<tr>
<td>45-64</td>
<td>3304</td>
<td>322</td>
<td>1.13</td>
<td>0.10</td>
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<td></td>
<td>(37.6)</td>
<td>(40.6)</td>
<td>(0.98-1.31)</td>
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<tr>
<td>≥65</td>
<td>2396</td>
<td>209</td>
<td>0.95</td>
<td>0.56</td>
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</tr>
<tr>
<td></td>
<td>(27.3)</td>
<td>(26.3)</td>
<td>(0.81-1.12)</td>
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**Sex**

<table>
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<tr>
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<th>Reference</th>
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<tr>
<td>Cases</td>
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<td>1797</td>
<td>592</td>
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<tr>
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<td>(79.5)</td>
<td>(20.5)</td>
<td>(74.6)</td>
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Excess alcohol

<table>
<thead>
<tr>
<th>Excess alcohol</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
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<td>1243</td>
<td>104</td>
<td>0.91</td>
<td>0.41</td>
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<td></td>
<td>Mean</td>
<td>Min-Max</td>
<td>p-values</td>
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</tr>
<tr>
<td>consumption</td>
<td>14.2</td>
<td>13.1</td>
<td>0.74-1.13</td>
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<tr>
<td>Smoker</td>
<td>1846</td>
<td>166</td>
<td>1.54</td>
<td>&lt;0.0</td>
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<tr>
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<td>21.0</td>
<td>20.9</td>
<td>1.31-1.81</td>
<td>01</td>
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<tr>
<td>TB contact</td>
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<td>0.00</td>
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<td>3.4</td>
<td>1.23-2.82</td>
<td>3</td>
<td>1.04-2.42</td>
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<tr>
<td>TB retreatment</td>
<td>1176</td>
<td>242</td>
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<td>30.5</td>
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</tbody>
</table>

- Excess alcohol consumption means ≥ 2 standard alcohol beverages per day.
- TB contact defined as contact with family members, schoolmates, or colleagues with TB.