Treatment outcomes of multidrug-resistant tuberculosis in Hangzhou, China, 2011 to 2015

Qingchun Li, MSa, Cynthia X. Shi, MSb, Min Lu, MSa, Limin Wu, BSc, Yifei Wu, MSa, Meng Wang, MSa, Le Wang, BSc, Gang Zhao, MD, PhDc, Li Xie, MSa, Han-Zhu Qian, MD, PhDc,d,f,∗

Abstract
Treatment of multidrug-resistant tuberculosis (MDR-TB) is challenging. More research is needed to understand treatment outcomes and associated factors.

A retrospective cohort study was conducted to assess trends and predictors of treatment success among 398 MDR-TB and extensively drug-resistant TB (XDR-TB) patients who started treatment in 2011 to 2015 in Hangzhou, China. Sociodemographic and clinical characteristic data were obtained from the national reporting database. Chi-square test for trend was used to evaluate changes in treatment success rates over the study years, and Cox regression analysis was used to identify predictors for poor treatment outcomes.

The treatment success rate was 76% (301/398) for all participants, 77% (298/387) for MDR-TB cases and 27% (3/11) for extensively drug-resistant tuberculosis -TB cases. Treatment success increased significantly from 66% among patients who started treatment in 2011 to 85% in 2015 (P < .01). Of the 97 (24.4%) patients with unsuccessful treatment outcomes, 10 (2.5%) died, 64 (16.1%) failed treatment, and 23 (5.8%) were lost to follow-up. Patients who started treatment in 2013 to 2015 were less likely to have unsuccessful outcomes than those who started in 2011–2012 (adjusted odds ratio [AOR] 0.4, 95% confidence interval [CI] 0.3–0.6), patients ≥25 years were more likely to have unsuccessful outcomes than younger patients (AOR 1.6, 95% CI 1.3–2.1), and cases with kanamycin resistance was associated with three times the odds of having unsuccessful outcomes than kanamycin-susceptible cases (AOR 3.0, 95% CI 1.5–5.8).

With proper case management of MDR-TB, patients can achieve a high treatment success rate. Hangzhou’s program offers clinical evidence that can be used to inform MDR-TB programs elsewhere in China and abroad.

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, DOTS = directly observed treatment, short-course, DST = drug sensitivity testing, INH = isoniazid, MDR-TB = multidrug-resistant tuberculosis, RIF = rifampin, TB = tuberculosis, TBIMS = tuberculosis information management system, WHO = World Health Organization, XDR = extensively drug-resistant tuberculosis.

Keywords: extensively drug resistant tuberculosis, multidrug-resistant tuberculosis, retrospective cohort study, treatment outcome

1. Introduction
China has one of the world’s heaviest burdens of drug-resistance tuberculosis (TB), and a better understanding is needed about the trends and treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB). In 2017, the World Health Organization (WHO) estimated that there were about 460,000 MDR-TB patients globally, and nearly half were in three countries: India (24%), China (13%) and Russia (10%). In China, 7.1% of new cases and 24% of previously treated cases were estimated to be multidrug- and
rifampicin-resistant TB, respectively.[10] The international community has committed to ending the TB epidemic by 2030.[14] Achieving this goal in China will require earlier detection of new infections, and prompt, complete, and effective treatment of all patients diagnosed with TB, particularly drug-resistant TB.

Global studies have shown that primary resistance due to direct transmission was the main source of drug resistance among TB patients.[15,16] Our 2015 study of 1326 tuberculous patients in eastern China found a similar drug-resistance pattern.[17] Effective and timely treatment renders MDR-TB patients rapidly noninfectious,[8] and this emphasizes the importance of proper treatment management as the key for reining in the MDR-TB epidemic.

Of MDR patients who receive a recommended WHO treatment regimen, less than 50% achieve treatment success;[13] this suboptimal context points to the need for newer drugs with greater efficacy and improved treatment delivery and management.[13] However, there are only 3 novel drugs for treating MDR-TB in the advanced stage of development, and nine in Phase 1 or Phase 2 trials.[9] Particularly since new medications are not yet available, the work of improving treatment outcomes must focus on improving diagnosis, treatment initiation, and clinical management of current drug regimens. Treatment success rates range from 34.5% to 81% globally,[10–14] and factors associated with failure of treatment included higher prevalence of XDR-TB, HIV co-infection, use of standardized treatment regimens rather than individualized ones, and incomplete or non-adherent treatment.[10,12,13,18] There is limited Chinese research on the outcomes of MDR-TB treatment.[19–22] In this study, we aimed to evaluate the trend of treatment success across time and to identify factors associated with unsuccessful treatment outcomes in a cohort of MDR/XDR-TB patients in Hangzhou, China.

2. Methods

2.1. Study setting, design, participants and database

Hangzhou is the capital city of Zhejiang Province in eastern China. It comprises 13 districts, one county-level city and two counties, and has 7.2 million local residents and over 2 million migrant population. There are thirteen hospitals that have TB care services; of these, there are two hospitals with the capacity to treat drug-resistant TB. We constructed this retrospective cohort study using de-identified information extracted from the Tuberculosis Information Management System (TBIMS), a national online database maintained by Chinese Center for Disease Control and Prevention (China).[23] Because TB is a notifiable disease in China, all diagnosed cases are reported to TBIMS, and this database serves as a central repository for TB diagnosis, treatment, and monitoring data. MDR-TB is defined as resistance to the two most common anti-TB drugs isoniazid (INH) and rifampin (RIF), and XDR-TB is defined as resistance to INH and RIF plus any fluoroquinolone and at least one of the three second-line injectable drugs (amikacin, capreomycin, and kanamycin).[13] This study includes nearly all diagnosed MDR-TB and XDR-TB patients who started treatment from 2011–2015 in Hangzhou. Patients were excluded from the study if they: were diagnosed with MDR-TB or XDR-TB but did not start treatment during the study period; were newly diagnosed; or did not have a documented treatment outcome. Variables abstracted from TBIMS were socio-demographic (gender, age, occupation, residence, ethnicity) and clinical information (eg, year of starting treatment, TB treatment history, results of sputum microscopy, culture and drug sensitivity testing [DST], duration of therapy, treatment outcome). Paper records were reviewed if a case’s electronic TBIMS record had missing data or logical errors. Personal identifiers were removed before data was used for analysis; no consent was obtained from individual TB patients. The study was approved by the ethics committee of Hangzhou City Center for Disease Control and Prevention.

2.2. TB diagnosis, treatment and management

Study participants were diagnosed and treated per the standard-of-care guidelines in Hangzhou, which were revised in 2010 and implemented with support from the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global Fund).[7] Sputum samples were collected before treatment initiation and examined through acid-fast bacilli smear microscopy and culture. DST was performed for all smear-positive TB patients and for all high-risk individuals, including patients with recurrent TB; close contacts of MDR-TB patients; patients who experienced treatment failure, relapse, or retreatment; and patients who remained smear-positive at the end of the second or third month of the initial treatment. Conventional biochemical tests for drug sensitivity test were performed using the proportion method on L-enstein-Jensen medium, with the following concentrations: 0.2 micrograms per milliliter (µ/mL) for INH, 40 µ/mL for RIF, 2.0 µ/mL for ethambutol, 2.0 µ/mL for ofloxacin, 4.0 µ/mL for streptomycin, and 30 µ/mL for kanamycin. The critical growth proportion for drug resistance was set at 1%. Additional details on TB diagnosis and DST are described elsewhere.[21]

All bacteriologically confirmed MDR-TB and XDR-TB patients were referred to MDR-TB-designated hospitals. Treatment regimens (standardized or individualized) were decided upon by a MDR-TB physician panel based on the patients’ DST results and history of previous TB treatment according to the National Guidelines of Chemotherapy of Drug-Resistant Tuberculosis.[24] Regimens included at least five drugs, including an injectable agent and fluoroquinolone, plus 2 to 3 second-line drugs (eg, cycloserine, protoniamid, aminosalicylate, ethionamide, thioacetazone) and any susceptible first-line drugs (eg, pyrazinamide, ethambutol, rifapentine, rifabutin). The duration of treatments was at least 24 months, including 6 to 12 months of the injection phase and 18 to 24 months of the continuous phase. According to the Directly Observed Treatment, short-course (DOTS) Plus guidelines, the patients received DOTS and monitoring for side effects by supervisors, who were doctors from local health care centers, hospital nurses, and trained family members. Patients attended monthly follow-up clinical examinations for sputum microscopy, culture, and prescription refills.

2.3. Treatment outcome definitions

According to the national guidelines,[24] treatment outcomes were assessed by physician panels in the MDR-TB-designated hospitals primarily based on the follow-up sputum microscopy, culture, and clinical monitoring. Study participant treatment outcomes were categorized as successful (cure or treatment completion) or unsuccessful (treatment failure, loss to follow-up, or death). Treatment outcomes were defined as follows: cure was defined as treatment completion and having ≥ 5 consecutive negative sputum cultures during the last 12 months of treatment or having ≥ 3 consecutive negative cultures following a positive
Table 1  
Cascade of diagnosis and treatment of multidrug-resistant tuberculosis in Hangzhou, China, 2011–2015.

| Year of starting treatment | Pulmonary TB diagnosed (1) | Smear positive screened (2) (% over (1)) | MDR/XDR diagnosed (3) (% over (2)) | MDR/XDR started treatment (4) (% over (3)) | MDR/XDR patients included in the study (5) (% over (4)) |
|---------------------------|---------------------------|-----------------------------------------|-----------------------------------|---------------------------------------------|------------------------------------------------------|
| 2011                      | 5158                      | 1850 (35.9)                             | 94 (5.1)                          | 68 (72.3)                                   | 68 (100.0)                                            |
| 2012                      | 5358                      | 1647 (30.7)                             | 162 (9.8)                         | 111 (68.5)                                  | 110 (99.1)                                            |
| 2013                      | 4806                      | 1805 (37.6)                             | 119 (6.6)                         | 94 (79.0)                                   | 94 (100.0)                                            |
| 2014                      | 4983                      | 1852 (37.2)                             | 74 (4.0)                          | 58 (78.4)                                   | 58 (100.0)                                            |
| 2015                      | 4776                      | 1652 (34.6)                             | 88 (5.3)                          | 73 (83.0)                                   | 68 (93.2)                                             |
| Total                     | 25081                     | 8006 (35.1)                             | 537 (6.1)                         | 404 (75.2)                                  | 398 (86.5)                                            |

MDR-TB = multidrug-resistant tuberculosis, TB = tuberculosis.

Culture. Treatment completion was defined as finishing the treatment regimen without evidence of failure but with inadequate bacteriological records to be defined as a cure, for example, <5 bacteriological exams during the last 12 months of treatment. Treatment failure was defined as ≥2 positive sputum cultures among the final five cultures, or one positive culture of the final three cultures during the last 12 months of treatment. Death was defined as all-cause mortality. Loss to follow-up was defined as having missed medical appointments for more than two consecutive months. Treatment outcome was defined a dichotomous variable: successful if patients were cured or completed treatment during the study years, and otherwise, unsuccessful. For all study participants who started treatment during 2011 to 2015, their treatment outcomes were assessed as of December 31, 2015.

2.4. Statistical analysis

In this retrospective cohort study, follow-up time was defined as the time from the date of initiating MDR-TB treatment to the date of finishing treatment. Time of censoring was defined as the time from the date of initiating MDR-TB treatment to the date of the last follow-up or December 31, 2015. Data on individuals known to have died or been lost to follow-up were censored at the date of death (if known) or the date of their last visit. Frequencies and proportions were used to summarize categorical variables, and medians were used to summarize continuous variables. Fisher’s exact test and Chi-square test for trend were performed to compare differences in treatment success rates over 5 calendar years. Cox regression model was fitted to identify predictors for unsuccessful treatment. Statistical significance was defined as a two-sided P value < .05. All statistical analyses were conducted using SPSS version 19.0.

3. Results

3.1. Demographic and clinical characteristics of participants

From 2011 to 2015, a total of 25,081 TB cases were diagnosed in Hangzhou, and 8,806 (35.1%) were sputum smear-positive. Of these positives, 537 (6.1%) were diagnosed as MDR/XDR TB cases. About three-quarters (N=404) of MDR/XDR TB cases started treatment. After excluding 5 patients who were still on treatment at the time of data extraction and one who had missing information, we included 398 patients in this analysis (Table 1).

Prior to treatment initiation, all participants were culture-positive, and 388 (97.5%) were smear-positive. Of the 398 participants, 387 (97.2%) had MDR-TB and 11 (2.8%) had XDR-TB. Table 2 summarizes the demographic and drug resistance characteristics: 71.4% were male, 76.4% were aged between 25–64, and 74.1% were farmers or migrant workers. The vast majority (92.7%) of participants had a history of TB treatment. The prevalence of resistance to individual TB drugs was: streptomycin 62.8%, ethambutol 44.2%, ofloxacin 10.3%, and kanamycin 5% (Table 2).

3.2. Treatment outcomes

In this study, the overall treatment success proportion was 75.6% (N=301) comprising 284 patients (71.4%) deemed cured and a further 17 (4.3%) who achieved treatment completion. Of all 398 patients, the mean duration of treatment was 22.5±3 months. The percentage of cases achieving culture conversion was 95.7% (N=381), and the mean time to culture conversion was 84.5 days (standard deviation [SD] 56.6). Of the 388 cases who were smear-positive at baseline, 378 (97.4%) achieved sputum smear conversion with a mean time to sputum smear conversion of 51.6 days (SD 42.1). Treatment success was significantly higher for 77.0% (N=298/387) for MDR-TB than for 27.3% (N=3/11) for XDR-TB participants (P<.01). Of 97 (24.4%) unsuccessful treatment cases, 10 (2.5%) died, 64 (16.1%) failed treatment, and 23 (5.8%) were lost to follow-up (Table 3). A significant positive trend for treatment success was observed among participants who started treatment from 66.2% in 2011 to 83.3% in 2015 (P<.01).

3.3. Predictors for unsuccessful treatment outcomes

Univariate analysis identified five factors that were significantly associated with an unsuccessful treatment outcome, including year of starting treatment, residence, age, occupation, and resistance to kanamycin. These variables were included in the multivariate analysis, and 3 factors were found to be independently associated with an unsuccessful treatment outcome: year of starting treatment in 2013 to 2015 (compared to years 2011–2012; adjusted odds ratio [AOR] 0.4; 95% confidence interval [CI] 0.3–0.6; P<.01), older age (≥25 years vs <25 years; AOR 1.6; 95% CI 1.3–2.1; P<.01), and resistance to kanamycin (AOR 3.0; 95% CI 1.5–5.8; P<.01). There was no statistical difference between migrants and local household registered residents (Table 4).
### Table 2
Characteristics of 398 MDR-TB patients in Hangzhou, China.

| Characteristics                                    | Total N = 398 (%) | MDR-TB N = 387 (%) | XDR-TB N = 11 (%) |
|----------------------------------------------------|-------------------|--------------------|-------------------|
| **Year of starting treatment**                      |                   |                    |                   |
| 2011                                               | 68 (17.1)         | 61 (15.8)          | 7 (63.6)          |
| 2012                                               | 110 (27.6)        | 109 (28.2)         | 1 (9.1)           |
| 2013                                               | 94 (23.6)         | 93 (24.0)          | 1 (9.1)           |
| 2014                                               | 58 (14.6)         | 57 (14.7)          | 1 (9.1)           |
| 2015                                               | 68 (17.1)         | 67 (17.3)          | 1 (9.1)           |
| **Residence**                                      |                   |                    |                   |
| Rural                                              | 163 (41.0)        | 160 (41.3)         | 3 (27.3)          |
| Urban                                              | 235 (59.0)        | 227 (58.7)         | 8 (72.7)          |
| **Registered household in Hangzhou**               |                   |                    |                   |
| No                                                 | 220 (55.3)        | 215 (55.6)         | 5 (45.5)          |
| Yes                                                | 178 (44.7)        | 172 (44.4)         | 6 (54.5)          |
| **Gender**                                         |                   |                    |                   |
| Male                                               | 284 (71.4)        | 275 (71.1)         | 9 (81.8)          |
| Female                                             | 114 (28.6)        | 112 (28.9)         | 2 (18.2)          |
| **Age, yr**                                        |                   |                    |                   |
| <25                                                | 59 (14.8)         | 58 (15.0)          | 1 (9.1)           |
| 25–44                                              | 171 (43.0)        | 168 (43.4)         | 3 (27.3)          |
| 45–64                                              | 133 (33.4)        | 127 (32.8)         | 6 (54.6)          |
| ≥65                                                | 35 (8.8)          | 34 (8.8)           | 1 (9.1)           |
| **Ethnicity**                                      |                   |                    |                   |
| Han                                                | 392 (98.5)        | 381 (98.5)         | 11 (100.0)        |
| Other                                              | 6 (1.5)           | 6 (1.5)            | 0 (0)             |
| **Occupation**                                     |                   |                    |                   |
| Farmer or migrant worker                            | 295 (74.1)        | 285 (73.6)         | 10 (90.1)         |
| Other                                              | 103 (25.9)        | 102 (26.4)         | 1 (9.1)           |
| **Positive sputum smear at baseline**              |                   |                    |                   |
| No                                                 | 10 (2.5)          | 10 (2.6)           | 0 (0)             |
| Yes                                                | 388 (97.5)        | 377 (97.4)         | 11 (100.0)        |
| **History of TB treatment**                        |                   |                    |                   |
| No                                                 | 29 (7.3)          | 29 (7.5)           | 0 (0)             |
| Yes                                                | 369 (92.7)        | 358 (92.5)         | 11 (100.0)        |
| **Resistance to streptomycin**                     |                   |                    |                   |
| No                                                 | 148 (37.2)        | 148 (38.2)         | 0 (0)             |
| Yes                                                | 250 (62.8)        | 239 (61.8)         | 11 (100.0)        |
| **Resistance to ethambutol**                       |                   |                    |                   |
| No                                                 | 222 (55.8)        | 221 (57.1)         | 1 (9.1)           |
| Yes                                                | 176 (44.2)        | 166 (42.9)         | 10 (90.9)         |
| **Resistance to ofloxacin**                        |                   |                    |                   |
| No                                                 | 357 (89.7)        | 357 (92.2)         | 0 (0)             |
| Yes                                                | 41 (10.3)         | 30 (7.8)           | 11 (100.0)        |
| **Resistance to kanamycin**                        |                   |                    |                   |
| No                                                 | 378 (95.0)        | 378 (97.7)         | 0 (0)             |
| Yes                                                | 20 (5.0)          | 9 (2.3)            | 11 (100.0)        |

MDR-TB = multidrug-resistant tuberculosis, TB = tuberculosis.

### Table 3
Treatment outcomes of MDR-TB patients in Hangzhou, China, 2011–2015.

| Year of starting TB treatment | Cure      | Treatment completion | Total     | Death | Failure | LTFU | Total     |
|-------------------------------|-----------|----------------------|-----------|-------|---------|------|-----------|
| 2011 (N=68)                   | 43 (63.2) | 2 (2.9)              | 45 (66.2) | 3 (4.4) | 16 (23.5) | 4 (5.9) | 23 (33.8) |
| 2012 (N=110)                  | 68 (61.8) | 8 (7.3)              | 76 (69.1) | 4 (3.6) | 23 (20.9) | 7 (6.4) | 34 (30.9) |
| 2013 (N=94)                   | 71 (75.5) | 6 (6.4)              | 77 (81.9) | 0 (0)  | 14 (14.9) | 3 (3.2) | 17 (18.1) |
| 2014 (N=58)                   | 45 (77.6) | 0 (0)                | 45 (77.6) | 1 (1.7) | 8 (13.8)  | 4 (6.9) | 13 (22.4) |
| 2015 (N=68)                   | 57 (83.8) | 1 (1.5)              | 58 (85.3) | 2 (2.9) | 3 (4.4)   | 5 (7.4) | 10 (14.7) |
| Total (N=398)                 | 284 (71.4)| 17 (4.3)             | 301 (75.6)| 10 (2.5)| 64 (16.1) | 23 (5.8)| 97 (24.4)|

Chi-square for trend: −3.011

P value: <.01

LTFU = loss to follow-up, MDR-TB = multidrug-resistant tuberculosis.
4. Discussion

The average success rate of MDR-TB treatment in Hangzhou was 75.6% among patients who started treatment during 2011 to 2015, peaking at 85% among patients started treatment in 2015. To our knowledge, this was the highest treatment success rate of MDR-TB patients to be reported in mainland China. This marks Hangzhou as the first Chinese city to achieve the WHO target of 75% treatment success. Treatment success rates reported in other Chinese cities were all under 70%, and the cure rate ranged from 50% to 60%. Our study reafirms a previous study that showed Hangzhou as having a higher MDR-TB treatment success rate (73.7%) than other areas of China. This study’s success rate is higher than rates seen in most resource-limited countries but lower than success rates of resource-rich counties. When compared to cure rates from other countries, we should note that the successful treatment rate in our study included both cure and completion of treatment according to Chinese guidelines; the successful treatment rate (75.6%) was slightly higher than the cure rate (71.4%).

This is the first study in China to report an increasing trend in successfully treating MDR-TB, which we observed across five years. This temporal improvement in treatment outcomes mirror a decline of MDR-TB prevalence during the same time period in Hangzhou. Improving treatment success and decreasing prevalence of MDR-TB in Hangzhou points to the need to prioritize effective treatment and management of MDR-TB cases in TB prevention and control programs. Studies have shown that MDR-TB is more likely to result from transmission rather than acquisition, and improved diagnosis and treatment of MDR-TB patients will reduce the spread of MDR-TB.

Table 4

| Variable                                      | N  | Unsuccessful outcome (%) | HR (95%CI) | P value | AHR (95% CI) | P value |
|-----------------------------------------------|----|--------------------------|------------|---------|--------------|---------|
| Year of starting treatment                    |    |                          |            |         |              |         |
| 2011–2012                                     | 178| 57 (32.0)                | 1.0        | <.001   | 1.0          | <.001   |
| 2013–2015                                     | 220| 40 (18.2)                | 0.4 (0.3, 0.7) | 0.4 (0.3, 0.6) |
| Residence                                     |    |                          |            |         |              |         |
| Rural                                         | 163| 49 (30.1)                | 1.0        |         |              |         |
| Urban                                         | 235| 48 (20.4)                | 0.6 (0.4, 0.9) |        |
| Gender                                        |    |                          |            |         |              |         |
| Male                                          | 284| 78 (27.5)                | 1.0        |         |              |         |
| Female                                        | 114| 19 (16.7)                | 0.7 (0.4, 1.1) |        |
| Age, yr                                       |    |                          |            |         |              |         |
| <25                                           | 59 | 3 (5.1)                  | 1.0        |         |              |         |
| ≥25                                           | 339| 94 (24.7)                | 1.7, 17.0  | 1.6 (1.3, 2.1) |
| Ethnic                                        |    |                          |            |         |              |         |
| Han                                           | 392| 96 (24.5)                | 1.0        |         |              |         |
| Other                                         | 6  | 1 (16.7)                 | 0.9 (0.1, 6.2) |        |
| Registered household in Hangzhou              |    |                          |            |         |              |         |
| No                                            | 220| 57 (25.9)                | 1.0        |         |              |         |
| Yes                                           | 178| 40 (22.5)                | 1.4 (0.9, 2.0) | 1.43    |
| Occupation                                    |    |                          |            |         |              |         |
| Other                                         | 103| 14 (13.6)                | 1.0        |         |              |         |
| Farmer or migrant worker                      | 295| 83 (28.1)                | 1.9 (1.1, 3.4) |        |
| Positive sputum smear at baseline             |    |                          |            |         |              |         |
| No                                            | 10 | 94 (24.2)                | 1.0        |         |              |         |
| Yes                                           | 388| 3 (30.0)                 | 1.2 (0.4, 3.7) |        |
| Previous TB smear at baseline                 |    |                          |            |         |              |         |
| No                                            | 29 | 3 (10.3)                 | 1.0        |         |              |         |
| Yes                                           | 369| 94 (25.5)                | 2.3 (0.7, 7.3) |        |
| Number of resistant drugs                     |    |                          |            |         |              |         |
| 2 (INH and RIF)                               | 99 | 24 (24.2)                | 1.0        |         |              |         |
| ≥2                                            | 299| 73 (24.4)                | 0.9 (0.6, 1.5) |        |
| Resistance to ethambutol                      |    |                          |            |         |              |         |
| No                                            | 222| 50 (22.5)                | 1.0        |         |              |         |
| Yes                                           | 176| 47 (26.7)                | 1.1 (0.8, 1.7) |        |
| Resistance to streptomycin                    |    |                          |            |         |              |         |
| No                                            | 148| 35 (23.6)                | 1.0        |         |              |         |
| Yes                                           | 250| 62 (24.8)                | 1.0 (0.6, 1.5) |        |
| Resistance to ofloxacin                       |    |                          |            |         |              |         |
| No                                            | 357| 83 (23.2)                | 1.0        |         |              |         |
| Yes                                           | 41 | 14 (34.1)                | 1.2 (0.7, 2.2) |        |
| Resistance to kanamycin                       |    |                          |            |         |              |         |
| No                                            | 378| 87 (23.0)                | 1.0        |         |              |         |
| Yes                                           | 20 | 10 (50.0)                | 2.6 (1.4, 5.1) | 3.0 (1.5, 5.8) |

AHR = adjusted hazard ratio, HR = hazard ratio, INH = isoniazid, MDR-TB = multidrug-resistant tuberculosis, RIF = rifampin.
Our study identified numerous predictors for an unsuccessful MDR-TB treatment outcome. Older age was associated with a poorer outcome, which is consistent with the literature. A British study showed that the mortality risk of MDR-TB patients can almost double for every 10-year increase in age, and another study showed that older patients have a higher incidence of co-morbidities that can worsen disease progression and increase the risk of poor outcomes. Kanamycin-resistant patients were also more likely to have an unsuccessful treatment outcome. Previous research has found that susceptibility to kanamycin quadrupled the likelihood of culture conversion, which is a prognostic marker of successful treatment; thus, resistance to kanamycin may decrease the chance of culture conversion. Patients who started treatment during 2011–2012 were more likely to have an unsuccessful treatment outcome compared to those who started in 2013–2015, and we attribute this to improved implementation of the MDR-TB treatment program in later years under the DOTS-Plus program—a DOTS program with components for MDR-TB diagnosis, management, and treatment.

Unsurprisingly, we found that XDR-TB cases had markedly worse outcomes compared to MDR-TB. Only 3 of 11 XDR-TB cases (27%) achieved a successful treatment outcome, which is consistent with studies elsewhere in China reporting 9–30% cases (27%) achieved a successful treatment outcome, which is worse outcomes compared to MDR-TB. Only 3 of 11 XDR-TB patients were also more likely to have an unsuccessful treatment outcome.

China's healthcare infrastructure and trained workforce capacity are not on par with those of fully developed nations, and in this resource-limited context, it is a laudable achievement for Hangzhou's TB control program to have met the WHO's target for MDR-TB treatment success. We suggest several reasons for the high successful treatment rate in Hangzhou from 2011 to 2015. First, the vast majority of MDR-TB cases were treated at the Zhejiang Province Center for TB Diagnosis and Treatment, which is located in the Hangzhou Red Cross Hospital. A MDR-TB physician panel developed individualized treatment plans for MDR-TB patients, which is likely to reduce misdiagnosis and mistreatment risks. Second, Hangzhou Center for Disease Control and Prevention had a designated staff member in charge of follow-up for MDR-TB patients and coordinating treatments between the Hangzhou Red Cross Hospital and Community Health Centers, and physicians in Community Health Centers established 1-to-1 treatment relationships with patients. Third, studies have shown that treatment cost is a strong predictor for treatment adherence and outcome of MDR-TB cases. The Global Fund in China invested heavily in scaling-up access to diagnosis and treatment of MDR-TB during the study years, and this program covered all costs of MDR-TB treatment, including patient transportation, which had a significant impact on initiation and adherence. Notably, migrant workers in China typically face challenges in accessing healthcare, but in our study, there was no statistical difference in treatment success between migrants and local residents due to the equitable financial coverage from the Global Fund. Hangzhou’s experience offers valuable and timely guidance on how to strengthen MDR-TB control in China. By studying, adapting, and implementing Hangzhou’s TB treatment guidelines and practices, other Chinese cities could improve the treatment outcomes of MDR-TB patients. However, while we are optimistic about the future of MDR-TB control in Hangzhou, we also urge caution in interpreting and generalizing these results. China has transitioned from being a Global Fund recipient to a Global Fund donor in the past five years, and as of 2018, only 2% of TB financing was drawn from international sources, which means that the financing for TB programs relies on the Chinese government. In order to continue the progress made under the China-Global Fund partnership, China must commit to sustained funding for TB prevention and control programs, particularly MDR-TB.

Because this was a retrospective study design, we faced some limitations in data availability. First, some important variables such as adverse reactions, body mass index, specific treatment regimens, migration, co-morbidities, and HIV co-infection, which had been reported to be predictors of poor treatment outcomes elsewhee, were not available for inclusion in this study. Second, not all monthly sputum samples were obtained from each patient, and the missing information may be a source of misclassification bias.

This study showed that Hangzhou has achieved high success in achieving treatment success for MDR-TB and has met the WHO treatment target. Treatment success rates increased from 2011 to 2013, which suggests improved implementation of MDR-TB control programs. With proper treatment and management of MDR-TB and XDR-TB, other Chinese programs could also improve treatment outcomes by adopting practices shown to be effective in Hangzhou.

Author contributions
Conceptualization: Qingchun Li, Han-Zhu Qian
Formal analysis: Qingchun Li, Cynthia X. Shi
Funding acquisition: Qingchun Li
Investigation: Qingchun Li, Min Lu, Limin Wu, Meng Wang, Le Wang
Laboratory tests: Yifei Wu
Project administration: Li Xie
Supervision: Gang Zhao, Han-Zhu Qian
Writing – original draft: Qingchun Li
Writing – review & editing: Cynthia X. Shi, Han-Zhu Qian.

References
[1] Liao S, Cai C, Huo FM, et al. Trends in drug-resistant tuberculosis in China: data from a clinical tuberculosis centre. Int J Tuberc Lung Dis 2017;21:990–5.
[2] Huang Y, Wu Q, Xu S, et al. Laboratory-based surveillance of extensively drug-resistant tuberculosis in Eastern China. Microb Drug Resist 2017;23:336–40.
[3] World Health OrganizationGlobal Tuberculosis Report 2018. Geneva: World Health Organization; 2018.
[4] Harries AD, Lin Y, Kumar AMV, et al. What can National TB Control Programmes in low- and middle-income countries do to end tuberculosis by 2030? F1000Res 2018;7:1011.
[5] Emily A Kendall, Mariam O Ofotan, David W Dowdy. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. Lancet Respir Med 2015;3:963–72.
[6] Yang C, Shen X, Peng Y, et al. Transmission of Mycobacterium tuberculosis in China: a population-based molecular epidemiologic study. Clin Infect Dis 2015;61:219–27.

[7] Li Q, Zhao G, Wu L, et al. Prevalence and patterns of drug resistance among pulmonary tuberculosis patients in Hangzhou, China. Antimicrob Resist Infect Control 2018;7:61.

[8] Dharmadhikari AS, Mphephile M, Venter K, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 2014;18:1019–25.

[9] Tiberi S, Plessis ND, Walzl G, et al. Tuberculosis: progress and advances in development of new drugs, treatment regimens, and host-directed therapies. Lancet Infect Dis 2018;18:e183–98.

[10] Parmar MM, Sachdeva KS, Dewan PK, et al. Unacceptable treatment outcomes and associated factors among India’s initial cohorts of multidrug-resistant tuberculosis (MDR-TB) patients under the revised national TB control programme (2007-2011): evidence leading to policy enhancement. PLoS One 2018;13:e0193903.

[11] Trenburg A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 2018;22:17–25.

[12] Bastos ML, Cosme LB, Fregona G, et al. Treatment outcomes of MDR-tuberculosis in patients in Brazil: a retrospective cohort analysis. BMC Infect Dis 2017;17:718.

[13] Gaddah MA, Mokhtar A, Rady M, et al. Prognostic factors of treatment outcome among patients with multidrug-resistant tuberculosis in Egypt. J Formos Med Assoc 2016;115:997–1003.

[14] Phuong NT, Nhung NV, Hoa NB, et al. Management and treatment outcomes of patients enrolled in MDR-TB treatment in Viet Nam. Public Health Action 2016:6:25–31.

[15] Kuhari J, Smith C, Khanezrav A, et al. Impact of pyrazinamide resistance on multidrug-resistant tuberculosis in Karakalpakstan, Uzbekistan. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 2018;22:544–50.

[16] Yin J, Yuan J, Hu Y, et al. Association between directly observed therapy and treatment outcomes in multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One 2016;11:e0150511.

[17] Kibret KT, Muges M, Memtah P, et al. Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies. Infectious diseases of poverty 2017;6:7.

[18] Weiss P, Chen W, Cook VJ, et al. Treatment outcomes from community-based drug resistant tuberculosis treatment programs: a systematic review and meta-analysis. BMC Infect Dis 2014;14:333.

[19] Alene KA, Yi H, Vinoy K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug resistant tuberculosis in Huan Province, China. BMC Infect Dis 2017;17:573.

[20] Xu C, Pang Y, Li R, et al. Clinical outcome of multidrug-resistant tuberculosis patients receiving standardized second-line treatment regimen in China. J Infect 2018;76:498–53.

[21] Zhang L, Meng Q, Chen S, et al. Treatment outcomes of multidrug-resistant tuberculosis patients in Zhejiang, China, 2009–2013. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2018;24:381–8.

[22] Fan YM, Ding SP, Bao ZJ, et al. Prognostic factors for treatment success in patients with multidrug-resistant tuberculosis in China. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease 2018;22:300–5.

[23] Huang F, Cheng S, Du X, et al. Electronic recording and reporting system for tuberculosis in China: experience and opportunities. J Am Med Inform Assoc 2014;21:938–41.

[24] Chinese Antituberculosis Association Guidelines for chemotherapy of drug-resistant tuberculosis(2009). Chin J Tuber Respir Dis 2010;33:485–97.

[25] Yin J, Wang X, Zhou L, et al. The relationship between social support, treatment interruption and treatment outcome in patients with multidrug-resistant tuberculosis in China: a mixed-methods study. Trop Med Int Health 2018;23:668–77.

[26] Lv L, Li T, Xu K, et al. Sputum bacteriociation conversion and treatment outcome of patients with multidrug-resistant tuberculosis. Infect Drug Resist 2018;11:147–54.

[27] WHOTowards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. Geneva: World Health Organization; 2011.

[28] Liao Deliang, Tao Weiguo, Zhang Lipeng, et al. Analysis of the efficacy and its influencing factors on multidrug-resistant tuberculosis in Shenzhen city. Chin J Antituberc 2017;39:184–90.

[30] Zhou Yinfa, Zhang Shanying, Liu Zhenni, et al. Analysis on characters of 242 patients with multidrug-resistant tuberculosis and the factors influencing their treatment outcomes. Chin J Antituberc 2017;39:1218–22.

[31] Du Yh, Su Rd, Zhou Hx, et al. Analysis of the factors affecting the treatment outcome of 116 multidrug-resistant pulmonary tuberculosis patients. Chinese Journal of Antituberculosis 2012;34:19–21.

[32] HE GX, Xie YG, Wang LX, et al. Follow-up of patients with multidrug resistant tuberculosis four years after standardized first-line drug treatment. PloS One 2010;5:e10799.

[33] Gaborit B, Revest M, Roblot F, et al. Characteristics and outcome of multidrug-resistant tuberculosis in a low-incidence area. Med Mal Infect 2018;48:457–64.

[34] Velayutham B, Nair D, Kannan T, et al. Factors associated with sputum culture conversion in multidrug-resistant pulmonary tuberculosis. Int J Tuberc Lung Dis 2016;20:671–7.

[35] Janmans AK, Aggarwal D, Dhillon R. Factors predicting treatment success in multi-drug resistant tuberculosis patients treated under programmatic conditions. IJTB 2018;6:135–9.

[36] Harraus EP, Garcia-Prats AJ, Law S, et al. Treatment and outcomes in children with multidrug-resistant tuberculosis: a systematic review and individual patient data meta-analysis. PLoS Med 2018;15:e1002591.

[37] van Altena R, de Vries G, Haar CH, et al. Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000–2009. Int J Tuberc Lung Dis 2015;19:406–12.

[38] Drobniwski F, Eltringham I, Graham C, et al. A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK. Thorax 2002;57:810–6.

[39] Gayoso R, Daltonmo M, Braga JU, et al. Predictors of mortality in multidrug-resistant tuberculosis patients from Brazilian reference centers, 2005 to 2012. Braz J Infect Dis 2018;22:305–10.

[40] Kurbatova EV, Cegelski JP, Lienhardt C, et al. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. Lancet Resp Med 2015;3:201–9.

[41] Pang Y, Li J, Huo F, et al. Prevalence and treatment outcome of extensively drug-resistant tuberculosis plus additional drug resistance from the National Clinical Center for Tuberculosis in China: a five-year review. J Infect 2017;75:433–40.

[42] Zhao M, Li X, Xu P, et al. Transmission of MDR and XDR tuberculosis in Shanghai, China. PLoS One 2009;4:e3730–14730.

[43] Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. N Engl J Med 2012;366:2161–70.

[44] Wang L, Li R, Xu C, et al. The Global Fund in China: Multidrug-resistant tuberculosis nationwide programmatic scale-up and challenges to transition to full country ownership. PLOS One 2017;12:e0177536.

[45] Shah NS, Auld SC, Brust JCM, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. N Engl J Med 2017;376:243–53.

[46] Hu H, Chen J, Sato KD, et al. Factors that associated with TB patient admission rate and TB inpatient service cost: a cross-sectional study in China. Infect Dis Poverty 2016;5:4.

[47] Chen Y, Zhao Y. Multidrug-resistant tuberculosis in rural China: lack of public awareness, unaffordable costs and poor clinical management. BMJ Case Rep 2018;bc12018323794.

[48] Long Q, Qu Y, Lucas H. Drug-resistant tuberculosis control in China: progress and challenges. Infect Dis Poverty 2016;5:9–19.

[49] Minghui R, Scano F, Sozi C, et al. The Global Fund in China: success beyond the numbers. Lancet Glob Health 2015;3:e75–7.

[50] Samuel JF, Sood A, Campbell JR, et al. Treatment interruption and treatment outcomes in multidrug resistant tuberculosis: a systematic review and meta-analysis. Sci Rep 2018;8:4980.