



Major article

Status of drug-resistant tuberculosis in China: A systematic review and meta-analysis



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Key Words:

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microbial susceptibility tests
prevalence
China

Background: We conducted a systematic review and meta-analysis on drug-resistant tuberculosis in China to provide useful data for tuberculosis (TB) surveillance and treatment.

Methods: Several databases, including PubMed, Embase, and the Chinese Biological Medical Database, were systematically searched between January 1, 1999, and August 31, 2015, using strict inclusion and exclusion criteria.

Results: The corresponding drug-resistant TB prevalence between the new and previously treated cases was significantly different in almost all of the economic regions. The Eastern coastal region is the most developed economic region with the lowest total drug-resistant TB prevalence (any drug resistance: 28%; 95% confidence interval [CI], 25%-32%; multidrug resistance: 9%; 95% CI, 8%-12%) and the lowest number of new cases (any drug resistance: 21%; 95% CI, 19%-23%; multidrug resistance: 4%; 95% CI, 3%-5%). The Northwest is the least developed area with the lowest drug-resistant TB prevalence for previously treated cases (any drug resistance: 45%; 95% CI, 36%-55%; multidrug resistance: 17%; 95% CI, 11%-26%). The prevalence (multidrug and first-line drug resistance) exhibited a downward trend from 1996-2014. The extensively drug-resistant prevalence in China was 3% (95% CI, 2%-5%) in this review.

Conclusions: Overall, the status of drug-resistant tuberculosis in China is notably grim and exhibits regional epidemiologic characteristics. We are in urgent need of several comprehensive and effective control efforts to reverse this situation.

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Tuberculosis (TB) is one of the most critical public health problems in the world, posing threat on an increasing number of people in recent years. As the second leading cause of death from a contagious disease just after AIDS,¹ TB claimed 1.5 million lives in 2014 according to the latest World Health Organization (WHO) report.² Although many efforts have been made for the last 2 decades to control this global disease, there were still an estimated 9 million

new incident cases of TB all over the world last year. The emergence of drug-resistant TB, especially multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB, pose another substantial threat of TB control.^{3,4}

MDR TB, defined as resistance to at least rifampicin and isoniazid,⁵ makes TB a more stubborn disease and further decreases the chance of successful treatment and survival. XDR TB, which is MDR plus resistance to any fluoroquinolone and at least one second-line injectable agents (capreomycin, kanamycin, or amikacin), also decreases the chance of a successful treatment and survival.⁶ Efficacious treatment of TB requires a prompt diagnosis and initiation of treatment, long-term monitoring, and care, which is difficult to conduct, especially in resource-poor countries.⁷ In recent years, increasing studies have demonstrated an association between TB incidence and the local economy.⁸⁻¹⁰ Moreover, annual incidence of drug-resistant TB in countries such as the United States

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is dramatically lower than that in countries in regions such as Sub-Saharan Africa and Asia,¹¹ suggesting a potential relation between drug-resistant TB and local economic status.

China has the largest number of TB and MDR TB cases in the world. According to the 2014 WHO global TB report, there were 480,000 incident cases of MDR TB worldwide. China ranked first, with an estimated total number of 130,548 cases.² China is a developing country with an incredibly uneven regional economy. Influenced by the vast territory and extremely unbalanced regional economy, the drug-resistant TB prevalence status in China is very complicated. The whole drug-resistant rate reported by the WHO is quite inadequate for TB control for China. Therefore, our team conducted a systematic review and meta-analysis on drug-resistant TB by region to provide more reasonable data for TB surveillance and treatment. Additionally, the huge number of drug-resistant TB cases and diverse local economic status make China a perfect model for researching the association between drug-resistant TB incidence and the economy, which would provide basic data for TB surveillance and treatment worldwide. We first analyzed the collected data in the 8 economic regions to identify the potential association between drug-resistant TB and local economic status in China.

MATERIAL AND METHODS

Search strategy and selection criteria

All studies addressing drug-resistant TB in China between January 1, 1999, and August 31, 2015, were identified via a systematic search in PubMed, Embase, and the Chinese Biological Medical Database. The following search terms were used: tuberculosis (Medical Subject Headings [MeSH]), *Mycobacterium tuberculosis* (MeSH), drug resistance (MeSH), drug susceptibility, multidrug-resistant, any drug-resistant, extensively drug-resistant, China, and Chinese. These terms were used in combination with “and” or “or.” This study was approved by the ethical committee of West China Hospital, Sichuan University (judgment reference no. 198; 2014). The references of the included studies were also manually searched to identify additional relevant publications. The detailed selection criteria were as follows.

Inclusion criteria

Two reviewers independently performed the initial screening of titles and abstracts. A second screening was performed via a full-text review by the same reviewers. The studies were finally included via a cross-checking method. Disagreements were discussed to reach a consensus. A study was included in the meta-analysis if it satisfied the following criteria:

1. The study was about drug-resistant TB in China.
2. Drug resistance data for either new or previously treated cases, or both, were mandatory.
3. Tested drugs included at least 4 first-line anti-TB drugs (isoniazid, rifampin, ethambutol, and streptomycin).
4. Standard drug susceptibility testing (DST) methods included the proportion method, absolute concentration method, and BACTEC method.
5. A new case was defined as a patient who had never been treated or treated for <1 month, and a previously treated case was defined as a patient who had been treated for no less than 1 month.
6. MDR TB refers to strains that are resistant to at least isoniazid and rifampin, whereas XDR TB refers to MDR plus resistance

to at least 1 of the 3 injectable second-line drugs (amikacin, kanamycin, and capreomycin) and any fluoroquinolone.

Exclusion criteria

A study was excluded if it had any of the following items applied:

1. Studies focused only on non-*Mycobacterium tuberculosis* (MTB).
2. Studies only dealing with extrapulmonary TB.
3. Studies considering only a special group, such as childhood TB.
4. Studies considering only TB cases coinfecting with other diseases.
5. Studies that had not performed DST based on first-line anti-TB drugs or using nonstandard DST methods.
6. Review articles, congress abstracts, studies reported in languages other than English or Chinese, meta-analyses, or systematic reviews.
7. Duplicate publication of the same study, and studies available only as an abstract. When duplicate reports from the same study were identified, only the one with a larger sample size or the one with more detailed information (eg, sex ratio, age distribution) was included.

Data extraction

Two reviewers independently extracted the following data: first author, year of publication, study setting, study enrollment time, distribution of age and sex in the population, number of patients investigated, and drug-resistant status (any drug resistance, monodrug resistance, multidrug resistance). The prevalence of resistance to first-line anti-TB drugs was included as well. Data were extracted from all of the included studies independently. Inconsistencies between the reviewers were discussed to reach a consensus.

Statistical analysis

Analyses were performed by R3.1.1 software (Bell Laboratories, Madison, WI) and Excel 2007 (Microsoft, Redmond, WA). A drug-resistant rate and corresponding 95% confidence intervals (CIs) were used in our study. Heterogeneity among the included studies was assessed via Q and I^2 tests. Random effects models were applied. Sensitivity analyses were conducted by omitting individual studies sequentially and comparing the P value of pooled rates. The results were identified as credible when the corresponding P value of the pooled rates was not substantially different. Publication bias was examined using an Egger test. The results were considered to have no publication bias when $P > .05$.

Economic regions

According to the conception of economic regional division during the 11th Five-Year Plan, the mainland was divided into 8 zones: Northeast (Liaoning, Jilin, and Heilongjiang), Northern coastal (Hebei, Shandong, Beijing and Tianjin), Eastern coastal (Zhejiang, Jiangsu and Shanghai), Southern coastal (Guangdong, Fujian, and Hainan), Middle Reaches of Yellow River/Yellow Valley (Shaanxi, Shanxi, Henan, and Inner Mongolia), Middle Reaches of Yangtze River/Yangtze Valley (Hubei, Hunan, Jiangxi, and Anhui), Southwest (Sichuan, Yunnan, Guangxi, Guizhou, and Chongqing), and Northwest (Gansu, Xinjiang, Tibet, Ningxia, and Qinghai). The financial situations in the regions are shown in [Supplemental Table S1](#). Data were gathered from the National Bureau of Statistics of China.

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