Characteristics of Rifampicin-Resistant Tuberculosis Detection in China: 2015-2019

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Abstract

Background: The very high burden of rifampicin resistance tuberculosis (RR-TB) and the very low RR-TB cases detection are a major challenge that China has been faced since the implementation of Programmatic Management of Drug-resistant Tuberculosis in 2006. To deal with the challenge of inadequate detection of RR-TB cases, China expanded the scope of screening for RR and the application of rapid molecular drug susceptibility testing tools after 2015 and included it in the "13th Five-Year" National Tuberculosis Prevention and Control Program (2016-2020). This study analyzed the changes of RR-TB detection during 2015-2019.

Method: We used data from the national Tuberculosis Information Management System to descriptively analyze characteristics of RR-TB detection from 2015 to 2019.

Results: 68200 RR-TB cases were detected in 2015-2019, of which 48.1% were new cases. In 2019, the coverage rate of PMDT in prefectures nationwide reached 95.0%, an increase from 70.0% in 2015. The number and detection rate of RR-TB cases increased year by year, from 10019 and 14.3% in 2015 to 18623 and 28.7% in 2019, respectively. Of the bacteriologically confirmed TB cases, 81.9% were tested for RR, a considerable increase from 29.5% in 2015. Only 41.0% of RR-TB cases had FQs susceptibility testing performed in 2019, and this proportion has been declining year by year since 2016. The proportion of application of rapid molecular tools increased from 24.0% in 2015 to 67.1% in 2019, and the median days to obtain RR results was significantly shortened from 61 days (IQR 27–91) in 2015 to 15days (IQR 2–55) in 2019. In 2019, 76.0% of RR-TB cases were diagnosed as presumptive RR-TB in county-level hospitals.

Conclusions: After China modified the RR-TB detection policies, the screening rate of RR and the number of RR-TB cases increased significantly, the RR testing methods have been transformed into the vast majority of the utilization of rapid molecular tools. However, comprehensive measures should be implemented to close the gap in the detection of RR-TB cases. It is imperative to take FQs susceptibility testing seriously and effectively strengthen the laboratory capacity of county-level hospitals.

Background

Drug-resistant tuberculosis (TB) remains an important public health concern worldwide, especially rifampicin resistance TB (RR-TB), which is defined as any resistance to rifampicin, including mono-resistance, multidrug resistance, polydrug resistance [1]. In 2019, there were 465,000 RR-TB cases worldwide; while 56% were undetected. Even when the diagnosis was made, only 57% achieve a successful treatment outcome [2].

China is a country with a high burden of RR-TB. The number of RR-TB cases accounts for 14% of the world, ranking second after India. The rifampicin resistance (RR) rates of new and retreated TB cases were 7.1% and 23.0%, respectively, which were higher than the global levels of 3.3% and 17.7% [2]. China initiated Programmatic Management of Drug-resistant Tuberculosis (PMDT) in 2006 with the support of the Global Fund Project. By the end of June 2014, when the Global Fund Project closed in China, nearly one-third of the prefectures in 30 provinces (a total of 31 provinces) implemented PMDT nationwide [3, 4]. However, due to limited resources and personnel capabilities, the traditional phenotypic drug susceptibility testing (DST) was mainly used at this stage and only the drug susceptibility of RR high-risk groups was tested. Not only did it take longer to diagnose patients but also fewer RR-TB patients were detected [5]. In 2012–2014, China only detected 5.0%, 7.7% and 11.3% of RR-TB cases estimated by the World Health Organization (WHO) [6–8]. The very high burden of RR-TB and the very low RR-TB cases detection had been the major challenge facing China since the implementation of PMDT in 2006.

WHO's End TB Strategy calls for the early diagnosis of TB and for universal drug-susceptibility testing [9]. In order to achieve the goal of End TB Strategy and solve the issue of lower detection of RR-TB cases, when the Global Fund Project ended and since 2015, China modified the RR-TB detection policy to scale up drug resistance screening of high-risk groups of RR-TB to all bacteriologically confirmed TB. In particular, the "13th Five-Year National Tuberculosis Prevention and Control Program (2016–2020)" (13th Five-Year TB Program) adopted the expansion policy of RR-TB detection and called for the priority application of rapid molecular technology for drug susceptibility testing to shorten the diagnosis time. It is required that the screening rate of high-risk groups for RR reach 95% and achieve full coverage of PMDT by the end of the 13th Five-Year Plan in 2020 [10]. In order to fulfill the commitment of the political declaration of the first United Nations (UN) High-Level Conference on Tuberculosis held in 2018 [11], the Chinese government issued the "Stop Tuberculosis Action Plan (2019–2022)" in 2019 and set a more ambitious target for rifampicin resistance testing, which is to achieve 90% of bacteriologically confirmed TB cases screened for rifampicin resistance by 2022 [12].

Benefiting from the accumulated experience during the Global Fund Project and aggressive promotion of the national 13th Five-Year TB Program and the Stop TB Action Plan (2019–2022), the number of RR-TB cases detected in China has increased significantly every year since 2015. In order to better understand the changes of RR-TB detection in China after 2015 and provide evidence for the national drug-resistant TB prevention and control strategy, we present a review of the current status of RR-TB detection in China from 2015 to 2019 based on data of the national Tuberculosis Information Management System (TBIMS) [13], focusing on the RR screening rate, the number of RR-TB cases detected and the application of rifampicin resistance diagnostic tools as well as the change in the source of presumptive RR-TB cases. In view of the fact that fluoroquinolones (FQs) is another core anti-tuberculosis drug besides rifampicin, whether there is resistance to FQs has a great impact on the choice of chemotherapy regimens and treatment outcomes [14, 15]. Moreover, WHO defines at least 80% of bacteriologically confirmed TB patients undergoing rifampicin resistance testing and at least 80% of RR-TB patients undergoing FQs resistance testing as good testing coverage [2]. Therefore, we also analyzed fluoroquinolones resistance (FQR) among RR-TB patients.

Methods

Data sources

The data was extracted from the national TBIMS. The bacteriologically confirmed TB cases notified in the TBIMS and of which were diagnosed with RR-TB cases were included in our analysis from January 1, 2015 to December 31, 2019.

DST methods and procedure

China currently applies rapid molecular and traditional phenotypic diagnostic tools to test the susceptibility of anti-tuberculosis drugs. Rapid molecular assays include Xpert MTB/RIF (Xpert) and line probe assays (LPAs) which are recommended by the WHO [16] as well as domestically produced MeltPro TB assay (MeltPro) [17] and Genechip [18]. MeltPro can detect isoniazid, rifampicin, and FQ resistance. Gene chip can detect isoniazid and rifampicin resistance. Bacteriologically confirmed TB cases are the subjects of DST and at least rifampicin, isoniazid, FQ and second-line injection are tested for drug susceptibility. If rapid molecular methods available, rapid DST will be preferred.

The procedure of DST is first to diagnose whether a presumptive TB patient is bacteriologically confirmed and then perform DST on the bacteriologically confirmed TB patient using molecular or traditional testing tools. Specifically, county-level TB designated hospitals diagnose bacteriologically confirmed TB cases, of which counties equipped with Xpert conduct rapid RR testing for bacteriologically confirmed TB cases and then the confirmed RR-TB cases will be referred to the prefecture-level designated TB hospitals for DST of other drugs; those counties without Xpert need to

transport sputum smear-positive specimens or culture-positive strains to the prefecture-level TB designated hospitals for DST of rifampicin and other drugs.

Laboratory quality control

China has established a complete laboratory network system at the national, provincial, prefecture and county levels and has a sound quality assurance (QA) system [19]. Laboratories at all levels not only carry out quality control（QC）but also accept external quality assessment (EQA). All laboratories are qualified to carry out testing only after passing quality assessment. Laboratories that carry out DST need to undergo a proficiency test organized by the National Tuberculosis Reference Laboratory once a year. County-level laboratories that carry out sputum smear microscopy need to undergo blind re-examination by prefecture-level laboratories every quarter.

Definitions

A bacteriologically confirmed TB case refers to sputum smear positive, only culture positive or only positive molecular testing positive [20]. The presumptive RR-TB patient in this article refers to a TB patient who is bacteriologically confirmed. High-risk groups refer to at least one of the following: (a) chronic TB patients /failure of retreatment TB patients, (b) close contact with a known RR-TB patient, (c) new TB patients of initial treatment failure, (d) relapsed or returned TB patients or (e) new TB patients remaining sputum culture or smear positive at the end of the 2nd month after treatment [21].

Statistical analysis

Relevant data were derived from TBIMS and used a descriptive analysis method to compare the changes of RR-TB cases detection in 2015-2019. The enumeration data were described by component ratio or rate. The comparison of inter-annual differences was tested by chi-squared test. The measurement data were described by Median (Q1-Q3). The comparison of inter-annual differences was tested by non-parametric test. All P values are two-tailed; a value less than 0.05 was considered statistically significant. All statistical analyses were done with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

The Status of RR-TB detection and FQs resistance testing

A total of 68200 patients were detected in 2015–2019, of which 48.1% were new patients. Only 50.3% of all RR-TB patients were tested for FQs susceptibility. The number of RR-TB patients detected and the RR screening rate and the coverage rate of PMDT increased year by year. However, in 2015–2017, during the first 3 years when RR-TB cases detection strategy changed, the rising trend was not obvious and the RR screening rate even declined slightly in 2016. Since 2018, in the late period of the 13th Five-Year TB Program, there has been a significant increase. By 2019, the number of patients detected and the RR screening rate and the coverage rate of PMDT reached the highest level, 1.9 times(18623/10019), 2.8 times(81.9%/29.5%) and 1.4 times(95/70) that of 2015 respectively. The proportion of FQs susceptibility testing in RR-TB cases had been declining year by year since 2016, and was the lowest in 2019(Table 1).

Table 1
The status of RR-TB detection, FQs resistance testing and PMDT coverage in China, 2015–2019

Year	Number of RR-TB cases detected*			RR screening rate (%)			The proportion of FQs screening in RR-TB cases (%)			The prefecture-level coverage rate for PMDT (%)
	All	New cases	High-risk groups	All	New cases	High-risk groups	All	New cases	High-risk groups	
2015	10019	3971(39.6)	6048(60.4)	29.5	23.1	57.3	57.8	58.6	57.2	70.0
2016	11423	4564(40.0)	6859(60.0)	28.6	22.8	54.8	59.6	60.3	59.0	70.0
2017	13069	6227(47.6)	6842(52.4)	37.8	33.1	57.2	51.9	52.7	51.1	78.0
2018	15066	7807(51.8)	7259(48.2)	62.8	60.2	72.6	48.2	51.3	45.0	90.0
2019	18623	10204(54.8)	8419(45.2)	81.9	80.4	88.4	41.0	42.7	39.0	95.0
Total	68200	32773(48.1)	35427(51.9)	49.4	45.3	67.2	50.3	51.0	49.6	-

* The value in brackets is the proportion of new cases or high-risk groups in all patients in the same year

Comparison with the number of RR-TB patients estimated by the WHO

The rate of bacteriologically confirmed TB cases increased significantly from 31% in 2015 to 47% in 2019. At the same time, the number of RR-TB cases increased year by year. Comparing the number of detected RR-TB cases with the WHO estimate, it can be found that the gap narrowed year by year. The annual detection rates of RR-TB cases were 14.3%, 15.6%, 17.8%, 22.8% and 28.7% respectively (Fig. 1).

DST methods and time to RR results notification

From 2015 to 2019, 52.2% of all patients used traditional phenotypic DST which was slightly higher than that of rapid DST. Although traditional DST was the main method, the application of rapid DST increased year by year. Since 2018, the proportion of rapid DST has exceeded that of traditional DST. In 2019, the proportion of RR detected by rapid DST was 67.1%, which was 2.0 times of the traditional method(67.1%/32.9%). The changes in the proportion of applying rapid DST annually were significant (Chi-square trend test, $P < 0.0001$) (Table 2).

The time interval from the sputum smear results notification to the obtaining of rifampin susceptibility results reduced year by year. From 2015 to 2019, the median time was 61 days (IQR 27–91), 52 days (IQR 21–86), 44 days (IQR 9–81), 34 days (IQR 6–72), 15 days (IQR 2–55) respectively. There was significant difference in the time of obtaining DST results in each year (Kruskal Wallis test, $P < 0.0001$) (Fig. 2).

Change in the source of presumptive RR-TB cases

Table 2 also reveals the change in the source of presumptive RR-TB cases. During 2015–2017, the proportion of RR-TB cases diagnosed as presumptive RR-TB in county-level TB designated hospitals decreased year by year. But from 2018, this trend has reversed and showed a sharp rise, reaching a maximum of 76% in 2019. The change in the source of presumptive RR-TB annually was significant(*Pearson*'s chi-squared test,$P < 0.0001$).

Table 2
DST method and the source of presumptive RR-TB cases

	2015 (n = 10019)	2016 (n = 11423)	2017 (n = 13069)	2018 (n = 15066)	2019 (n = 18623)	Total (n = 68200)	P value
DST method							
Rapid	2407(24.0)	3714(32.5)	5623(43.0)	8378(55.6)	12501(67.1)	32623(47.8)	0.000
Traditional	7612(76.0)	7709(67.5)	7445(57.0)	6688(44.4)	6122(32.9)	35577(52.2)	
The source of presumptive RR-TB cases							
County-level hospital	6224(62.1)	6722(58.8)	7469(57.2)	11133(73.9)	14155(76.0)	45703(67.0)	0.000
Prefecture-level and above hospitals	3795(37.9)	4701(41.2)	5600(42.8)	3933(26.1)	4468(24.0)	22497(33.0)	

Discussion

This is the first time to analyze the characteristics of RR-TB case detection at the level of PMDT after 2015, especially after implementation of the national 13th five year TB Program in 2016 in China.

Our analysis indicated that the RR screening rate and the number of RR-TB cases detection have increased significantly from 2015 to 2020. In 2019, the screening rate of RR in all bacteriologically confirmed TB cases reached 81.9%, exceeding the global level of 61% [2] and has become a routine work of the National TB Program (NTP). Delay in the diagnosis of RR-TB is one of the important reasons for the death, loss and inappropriate treatment for RR-TB cases [22–24], as well as increases in the risk of drug resistance spreading in the community. The median days for RR-TB cases to obtain RR results have been significantly reduced to 15 days in 2019, which is lower than 26 days in South Korea [25]. Shanghai, China, a metropolis with a population of 30 million, the diagnosis time has been as short as 9 days [26].

The main reason for the above changes is that after the national drug resistant cases detection policy was modified, in order to achieve the national 13th Five-Year TB Program targets, the governments at all levels strengthened their commitment, especially near the end of the 13th Five-Year TB Program. This was done by increasing the capabilities of laboratories in weak areas and the aggressive scale up of the use of rapid molecular DST tools. From 2015 to 2018, the Chinese government has invested a total of about 260 million CNY to support economically underdeveloped areas such as the central and western regions to equip rapid molecular diagnostic tools [27]. Furthermore, China central government provided funds for transportation costs of the county-level sputum specimens and strains and raised funds from various sources to provide free screening costs for presumptive RR-TB cases. These comprehensive measures improved the detection of RR-TB. Although the RR screening rate among high-risk groups has not yet reached the target of the 13th Five-Year TB Program, it will be achievable given the right strategic focus complemented by sustained leadership and adequate resources in 2020.

Our analysis also revealed that the source of presumptive RR-TB cases has changed in 2015–2019. More and more presumptive RR-TB cases are diagnosed in county-level hospitals, and the proportion is as high as 76.0% in 2019. The main reason for this trend is that the 13th Five-Year TB Program called for improving TB graded diagnosis and treatment services in order to strengthen the integration of TB prevention and treatment and make more rational use of

medical resources [10]. By enhancing the capacity building of county-level TB designated hospitals and the differentiation of medical insurance reimbursement to guide patients visiting hospitals in their jurisdiction to improve the accessibility of health care. The finding is of significance to China's future deployment of PMDT. Although the diagnosis of drug-resistant TB is set at the prefecture level, it is necessary to include county-level rapid rifampicin susceptibility testing so that RR cases can receive appropriate treatment early and can reduce the spread of drug resistance. And only by improving the TB diagnosis capabilities of county-level hospitals can "missing RR-TB cases" be reduced.

Our analysis also found some issues about which to be concerned. First, the proportion of new RR-TB cases has reached 54.8% in 2019. New RR-TB cases represent primary rifampicin resistance, suggesting that we need to pay attention to the spread of drug-resistant tuberculosis. Some studies in China have shown the transmission of multidrug-resistant tuberculosis [28, 29]. Our analysis results also indicate that the potential risk of community transmission of RR-TB in China is relatively high in recent years. China currently has no legislation on isolation treatment or travel restrictions for infectious RR-TB cases. It is imperative that China explores the possibility of legislation to manage infectious RR-TB in the future.

A second key concern is the still low detection rate of RR-TB cases. 2019 was the year with the largest number of cases diagnosed, but only 28% of RR-TB patients estimated by WHO were detected. This suggests that more than 70% of RR-TB cases were being missed. The main reasons are firstly that the rate of bacteriologically confirmed TB cases in China was low. It was 47% in 2019, which is lower than the global rate of 57% [2]. Secondly, 5% of prefectures cannot carry out DST nationwide and 17% of the prefectures have just gained the ability for DST in 2018–2019. The likelihood of insufficient personnel capacity and experience will affect the patient's diagnosis. Thirdly, there are limitations on current drug- resistance diagnostic algorithms regarding utilization of the Xpert. Xpert is just a tool for the diagnosis of RR in bacteriologically confirmed TB in China and isn't used in the diagnosis of signs or symptoms of TB as recommended by the WHO to maximize the detection of TB and RR-TB cases [16]. Xpert is still an expensive tool for China because the number of people with presumptive TB symptoms in China is enormous (about 3 million people per year).

A third issue relates to the FQs susceptibility testing. Contrary to the increasing RR screening rate, FQs testing proportion has been declining year by year from 2016 and only 41.0% of RR-TB cases were tested for FQs susceptibility in 2019, which was far lower than 71% globally [2], and was lower than 44% in South Africa [30]. According to WHO's good susceptibility testing coverage standards, although China's RR screening rate has exceeded 80%, due to the low FQs susceptibility testing rate, China has not yet reached good testing coverage [2]. The main reason for the low proportion of FQs susceptibility testing is that the FQs screening rate is not a target indicator of the 13th Five-Year TB Program. Despite FQs susceptibility was tested, the result was not registered in the TBIMS in time. In addition, similar to the reason for the lower RR-TB detection, the DST capability of some newly implemented PMDT prefectures, especially second-line drug susceptibility testing, still need to be improved. Apart from the above two reasons, since FQs susceptibility testing is not free currently, this will also lead to a lower proportion of FQ testing.

FQ is the backbone of RR treatment regimens and FQs resistance is associated with poor treatment outcomes. WHO recommended that, before initiating treatment for RR-TB cases, it is necessary to carry out susceptibility testing for FQs, preferably by rapid assay [31].The resistance rate of FQs among RR-TB patients in China is 27.4% [32], which is higher than the global average of 21% [2]. This implies that at least 1/4 of RR-TB cases enrolled for treatment that have not undergone FQs susceptibility testing will have a risk of poor treatment outcomes. China has introduced the short-course chemotherapy regimen recommended by the WHO for 9–12 months. The key eligible criterion for using the short-term regimen is that the patient is not resistant to FQs. Therefore, in order to enable patients to apply appropriate

chemotherapy regimens to ensure the patient's therapeutic effect, it is imperative to conduct FQs susceptibility testing for RR-TB patients.

There are some limitations in our study. We used data from the TBIMS. The registration system only classifies the RR testing as “fast” and “traditional”, and it is not yet possible to distinguish whether the FQs susceptibility testing is “molecular” or “traditional”. If we need to understand the current ability of FQs rapid molecular DST in China, a special investigation needs to be conducted. In addition, the current system is unable to obtain data about whether the results of RR are directly diagnosed at the county level or by transporting specimens to prefectures for diagnosis. This data is meaningful for the national budget for the delivery of sputum specimens and the layout of rifampicin resistance testing institutions.

Conclusions

Our analysis demonstrated that the political commitment together with aggressive 13th Five-Year TB Program targets have a great impact on the detection of RR-TB cases in China. After the change in RR-TB detection policy, we have seen a significant increase in the screening rate of RR and the number of RR-TB cases. At present, screening of RR is a routine work of NTP. Nonetheless, there is still a gap in the detection of RR-TB cases. FQs susceptibility testing is another key concern in China’s current DST. In order to achieve the goal of END TB, China also needs to reduce the spread of RR-TB and effectively strengthen the laboratory capability at the county-level to allocate health resources reasonably.

Abbreviations

RR-TB: rifampicin resistance tuberculosis; PMDT: Programmatic Management of Drug-resistant Tuberculosis; DST: drug susceptibility testing; TBIMS: Tuberculosis Information Management System; FQs: fluoroquinolones; TB: tuberculosis; WHO: World Health Organization; 13th Five-Year TB Program: "13th Five-Year” National Tuberculosis Prevention and Control Program (2016-2020)"; Xpert: Xpert MTB/RIF; LPAs :line probe assays; MeltPro: MeltPro TB assay. NTP: National TB Program.

Declarations

Acknowledgements

Not applicable.

Authors’ contributions

SW, LR conceptualized the paper, SW drafted the manuscript, LR reviewed the paper, and RY participated in the data interpretation and discussion. LT, DX, JJ participated in data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

All data during this study are included in this published article.

Ethics approval and consent to participate

Our analysis is based on data from the national TBIMS and no ethical approval is required.

Consent for publication

We analyzed the data routinely collected by the National Tuberculosis Program, consent for publication is not applicable.

Competing interests

The authors declare no competing interests.

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Figures

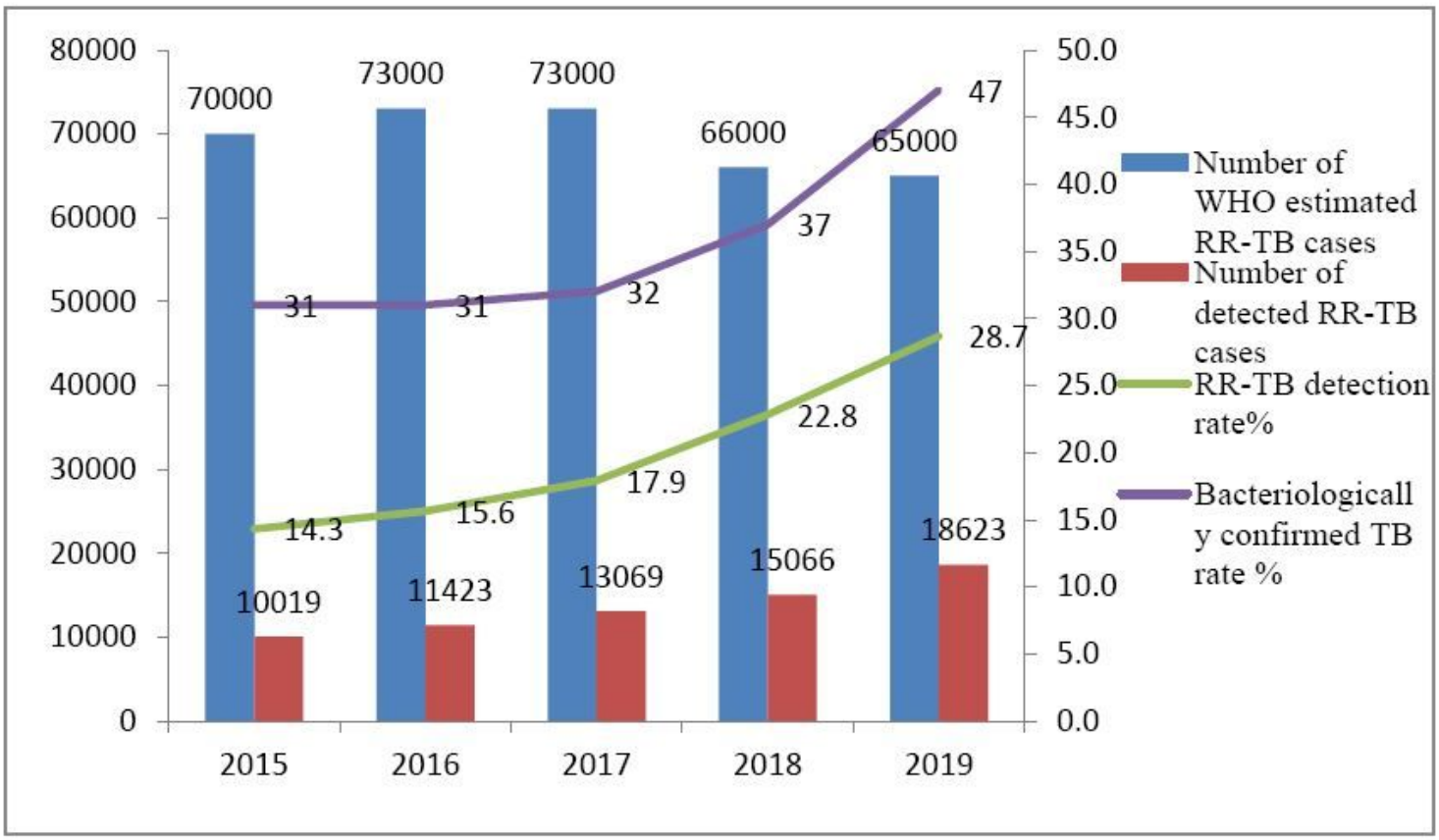

Figure 1

Comparison between the number of RR-TB cases detected and the WHO estimated, 2015-2019. Number of WHO estimated RR-TB cases, bacteriologically confirmed TB rate: from annual WHO TB report.

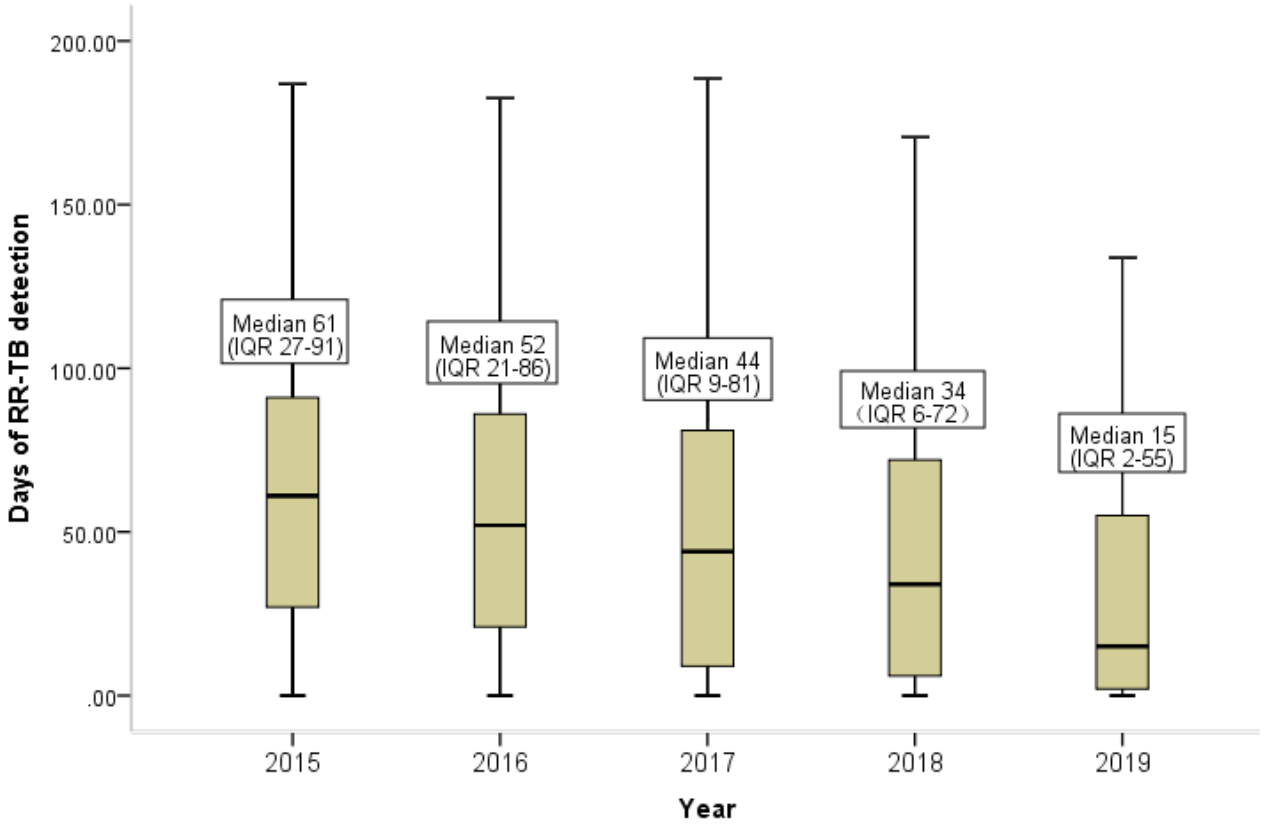

Figure 2

Days of RR-TB diagnosis: the time interval from the reporting time of sputum smear results to the reporting time of rifampicin susceptibility results.