

# Impact of Multiple Policy Interventions on the Screening and Diagnosis of Drug-Resistant Tuberculosis Patients: Cascade Analysis on 6 Cities from Eastern China

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## Research Article

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## Abstract

**Background** The detection of drug resistant tuberculosis (DR-TB) is a major concern in China. China has implemented multiple DR-TB interventions in partnership with development partners and via domestic policy reforms. We aim to summarize the interventions related to the screening and detection of DR-TB in Jiangsu Province, analyse their impact, and highlight policy implications for the prevention and control of DR-TB.

**Methods** We selected six prefectures across Jiangsu Province, a relatively developed area in China with a long history of collaboration with development partners and provincial policy reforms. We collected policy documents between 2008 and 2019, and extracted routine TB patient registration data from the TB Information Management System (TBIMS) between 2013 and 2019. We used the *High-quality Health System Framework* to guide the analysis. We performed statistical analysis on the percentage of pulmonary TB cases confirmed by bacteriology, percentage of bacteriologically confirmed TB patients tested for drug susceptibility by prefecture and by year. We used logistic regression models on TB cases confirmed by bacteriology and bacteriologically confirmed TB patients tested for drug susceptibility to further assess the impact of different policy interventions.

**Results** Our study found that three prefectures in Jiangsu introduced DR-TB related interventions between 2008 and 2010 in partnership with the Global Fund and the Bill and Melinda Gates Foundation. By 2017, all prefectures in Jiangsu had implemented provincial level DR-TB policies, such as increases in human resources for health, use of rapid molecular tests (RMT), expanded drug susceptibility testing (DST) for populations at risk of DR-TB, and allocation of funds specifically targeting DR-TB. With the use of RMT, the diagnostic process of DR-TB was optimized and the testing time shortened. The percentage of pulmonary TB cases confirmed by bacteriology increased from around 30% to over 50% between 2013 and 2019, indicating that the implementation of new diagnostics, including RMT, have provided more sensitive testing results than the traditional smear microscopy. At the same time, the proportion of bacteriologically confirmed cases tested for drug resistance has increased substantially, indicating that the intervention of expanding the coverage of DST has reached more of the population at risk of DR-TB. Prefectures that implemented interventions with the Global Fund and the Bill and Melinda Gates Foundation had better performance in detecting DR-TB patients. The disparities in detecting DR-TB among prefectures significantly narrowed after the implementation of provincial DR-TB polices.

**Conclusions** The introduction of new diagnostics, including RMT, have improved the detection of DR-TB. Prefectures implementing interventions with the Global Fund and the Gates Foundation had better detection of DR-TB even after the end of the partnership. Additionally, the implementation of provincial DR-TB polices led to improvements in the detection of DR-TB across all regions.

## Background

Tuberculosis (TB) is a communicable disease that remains a key global health concern. In 2017, it led to the highest number of deaths and the second highest Disability-Adjusted Life Years (DALYs) among all communicable diseases globally[1]. The End TB Strategy led by the World Health Organization endeavours to reduce TB deaths by 95% and eliminate catastrophic health expenditures caused by TB by 2035[2]. China has made great achievements in TB care and control: China's incidence of TB has been decreasing from 170/100 000 in 1990 to 61/100 000 in 2018[3]. However, drug-resistant TB (DR-TB) continues to remain a public health threat in China. A 2007 national survey reported that 5.7% of new TB patients and 25.6% of previously treated TB patients were infected with multidrug-resistant TB (MDR-TB) [4]. Comparing to regular TB, MDR/RR-TB is more resource intensive with a longer treatment course, but the treatment success rate is less than 60% globally [5, 6]. In 2018, less than one fourth of MDR/RR-TB patients were estimated to be detected, and of those that were detected, only 60% have initiated treatment [6].

Multiple strategies have been implemented in China to increase the detection of and treatment rates for DR-TB patients. In 2006, China started a partnership with the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) in two provinces. The partnership aimed to improve DR-TB diagnosis, treatment, and management[7]. Through another partnership in 2009 with the Bill & Melinda Gates Foundation (BMGF), rapid molecular tests (RMT) for DR-TB diagnosis and other treatment and financing interventions were piloted in four prefectures of four provinces in China [8, 9]. Given its rapid economic development, the Global Fund ended its partnership with China in 2014 and as a response to the end in external support, the Chinese government put more funding and policy support into DR-TB control and care. Since 2012, a national action plan has been announced to set goals on establishing a new financing mechanism for DR-TB control, regulating the use of second line TB drugs, establishing DR-TB treatment and management sites at the prefecture level, coordinating the health services for DR-TB, enhancing capacity building and implementing DR-TB case finding strategy[7, 10].

Provinces across China have implemented different TB strategies, and those that were supported by donor programs also introduced additional TB strategies. However, most of existing evidence provided assessment on single policy intervention on DR-TB, none has evaluated the impact of multiple interventions funded by domestic government and development partners. Wang et al summarized the implementation of projects funded by the Global Fund across China, but there was no assessment on the impact of different interventions[7]. Li et al evaluated the effect of a comprehensive DR-TB project with focus on access to diagnosis, quality treatment, and affordable treatment for MDR-TB[8]. Huang et al evaluated the benefit of expanding the diagnostic algorithm for diagnosis and treating bacteriologically confirmed pulmonary TB and RR-TB[11]. Considering the significant variance in DR-TB policies across the country and the various external factors beyond the health sector that may also influence DR-TB control and care, it is essential to understand the complexity of DR-TB interventions to further improve the DR-TB policies at both the national and provincial level. The purpose of this study is to summarize the interventions and policy changes in the screening and detection of DR-TB patients in Jiangsu Province, analyse their impact, and provide policy implications for the prevention and control of DR-TB. Jiangsu has a long history of DR-TB control through partnership with international organizations and domestic efforts, and ranked top-tier among all provinces in China for the detection of DR-TB. By examining DR-TB policies and their impact using real-world evidence from Jiangsu, useful insights on DR-TB control could be extended to other regions of China.

## Methods

### Settings

We selected Jiangsu province as our study site. Jiangsu lies on the east coast of China. It is the fourth wealthiest province in China, with a GDP per capita \$17,450 as of 2018. There are thirteen prefectures in Jiangsu Province with populations ranging from 3.2 million to 10.7 million. There is regional variance in economic development across the province, with prefectures in southern Jiangsu being the most developed followed by those located in central and northern Jiangsu. We selected Jiangsu province for several reasons. First, Jiangsu hosted one of the first project sites for international collaboration on DR-TB control and care, including collaborations with the Global Fund and BMGF. Second, the provincial and prefecture-level governments of Jiangsu were very supportive of the prevention and treatment for DR-TB. Finally, Jiangsu province has had digitalized Hospital Information System (HIS) and TB Information Management System (TBIMS) since 2005[12]. The accessibility and quality of historical data made our analysis feasible.

We selected two prefectures from each region of Jiangsu Province to ensure representation of the different levels of development and reflect variation among local policies: Zhenjiang and Changzhou (South), Nantong and Yangzhou (Central), Huai'an and Lianyungang (North). Socioeconomic information of selected prefectures can be found in Appendix 1a.

### Conceptual framework

We used the *High-quality Health System Framework* to guide the analysis[13]. We first looked at the *Foundations* that have been invested and used in DR-TB prevention and treatment, including policy, workforce, diagnostic devices, etc. Then, we described the *Processes* of care that indicated the activities for DR-TB testing, such as turnaround time for testing results. Finally, we presented the percentage of pulmonary TB cases confirmed by bacteriology and the percentage of bacteriologically confirmed TB patients tested for drug susceptibility as the *Impact* indicators of the DR-TB interventions.

### Data collection

We collected government policy documents related to prevention, screening, diagnosis, and management of DR-TB. We also collected the protocols of DR-TB related projects from 2008 to 2019 at provincial, prefecture, and county levels to understand the interventions by project funders as well as the policies issued by local government. We collected notified TB cases and presumptive DR-TB patients from TBIMS[12]. Data were restructured into three case-based databases: one for all active TB cases, one for patients with presumptive DR-TB, and one for confirmed DR-TB cases.

We extracted notified TB case records and presumptive DR-TB case records from TBIMS from the six selected sites. Records with a diagnosis of "pulmonary tuberculosis" between Jan 1, 2013 and Dec 31, 2019 were included for analysis. We collected the following indicators for notified TB patients (i.e., those with pulmonary TB): registration number, age, sex, residency (within the county, within the prefecture, etc.), and TB related information including bacteriological results, previous TB treatment, whether diagnosed at county or prefecture agency, type of diagnosis agency, and date of entry (into TBIMS). Similarly, we collected the following indicators for presumptive DR-TB: diagnosis region, registration number, age, sex, source of presumptive DR-TB (linked with TB database, directly registered and linked with confirmed DR-TB database), the registration date of basic management unit (BMU)[14, 15], smear results,

culture results, strain identification results, types of drug susceptibility testing (DST) (phenotypic or genotypic), results of DST, confirmed date of DST, and date of entry. No personally identifiable information was extracted from the database.

## Data analysis

Descriptive analysis on key indicators was disaggregated by year and by prefecture. The definitions of key indicators of interest are listed below.

- 1) Bacteriologically confirmed TB case: A patient from whom a biological specimen is positive by smear microscopy, culture, or rapid diagnostic test.
- 2) Percentage of pulmonary TB cases confirmed by bacteriology: The number of bacteriologically confirmed TB cases divided by the number of notified active pulmonary TB cases.
- 3) Percentage of bacteriologically confirmed TB patients tested for drug susceptibility: The number of bacteriologically confirmed TB cases tested for drug resistance (including tested only for rifampicin resistance) divided by the number of bacteriologically confirmed TB cases.
- 4) Suspected high risk (M)DR-TB patients[7]: TB patients with at least one of the following conditions: a) failure to respond to the initial or retreatment efforts, chronic cases of TB, b) close contact with a known MDR-TB patient, c) smear-positive at the end of 2 to 3 months of initial treatment.

We used logistic regression models on notified TB records to further assess the impact of different policy interventions. In model 1, the dependent variable was the bacteriological results. The key explanatory variable was use of the new diagnostic devices. The control variables were: year of registry (data must be entered within 24 hours of diagnosis), prefecture, sex, age group (under 45, 45 to 60, and over 60), treatment history (new patient, previously treated patient), cavitary disease (no, yes), administrative level of diagnosis agency (prefecture, county), type of diagnosis agency (general hospital, specialized hospital, CDC clinic or TB dispensary), current residency (within county, within prefecture, within Jiangsu, outside Jiangsu). For model 2, the dependent variable was confirmed TB patients tested for drug susceptibility. We used a group of dummy variables as a key explanatory variable to indicate the interventions on the DST coverage, while the control variables were the same as model 1.

## Results

### 1 Policies and major interventions

Based on our review of the policy documents and intervention protocols, we mapped out different TB interventions that were implemented in each prefecture between 2013 and 2019. Considering the impact of health interventions may last longer after its implementation, we summarized the DR-TB related interventions between 2008–2019.

Figure 1 shows the timeline, scope of each intervention, and implementation sites of major interventions related to the screening and diagnosis of DR-TB. Zhenjiang was the first prefecture to implement DR-TB interventions on treatment and patient management (Global Fund, 2008–2014), followed by Lianyungang and Nantong. These three prefectures started to follow provincial level DR-TB interventions after the end of international projects. Conversely, Changzhou, Huai'an, and Yangzhou, implemented DR-TB interventions relatively late, beginning only in 2012. In contrast to the other three prefectures of focus, these three prefectures did not host any TB-related international projects, and therefore only implemented provincial level DR-TB interventions.

The main interventions supported by the Global Fund project from 2008 to 2014 in Jiangsu (Fig. 1) included: DST with smear-positive patients; covering the cost of hospital admission for MDR-TB treatment; providing MDR-TB patients with a transport subsidy; and ensuring a consistent supply of second-line drugs. The first phase of the China-Gates project focused on improving MDR/RR-TB diagnosis, treatment, financing, and DST with smear positive patients. The second phase of the China-Gates focused on setting a comprehensive TB control model for effective diagnosis, treatment, and management of TB patients using the molecular diagnosis technology and expanding DST coverage[16]. At the beginning of the provincial project, it focused on diagnosis, treatment, management, financing of MDR-TB patients, and DST with suspected high risk (M)DR-TB patients. To accelerate the pace of TB control, RMT was introduced to all TB labs by 2017 and DST with bacteriologically confirmed TB cases.

### 2 Workforce and funding for DR-TB

We reviewed and compared the changes in TB related staff, funding for DR-TB and laboratory equipment between 2013 and 2018 as the input of DR-TB detection. Between 2013 and 2018, the number of designated TB hospitals remained the same for most prefectures except for Zhenjiang, while the number of RMT devices have been increased substantially, indicating more TB designated TB hospitals were facilitated with RMT devices (Appendix 1b). In 2013, there were only three TB laboratories equipped with RMT devices: by 2018 all TB laboratories were equipped with RMT devices, funded either by international programs or provincial government. Between 2013 and 2018, the number of full-time staff at local CDCs dropped slightly while that of the designated TB hospitals increased. Full-time staff of local CDCs declined in five prefectures, with the greatest declines found in Zhenjiang and Nantong. Between 2013 and 2018, full-time staff of designated TB hospitals increased in most prefectures, among which Yangzhou saw the most growth (from 32 to 71). Funds allocated specifically for DR-TB control and prevention from the provincial government increased substantially in five prefectures and the disparity of special funds dedicated to DR-TB narrowed in 2018: Lianyungang was the only prefecture that saw a decline in special funds and Nantong had the most rapid growth, followed by Zhenjiang and Huai'an (Appendix 1b).

### **3 Screening and testing process**

Screening and testing are regarded as inter-mediate changes of DR-TB detection practice. As mentioned in previous sections, more devices have been put into use in Jiangsu while the detection population has been expanded according to some DR-TB detection polices. We compared the screening and testing process for DR-TB between 2013 and 2019 to observe changes.

Conventional diagnosis methods (including sputum smear microscopy, culture and phenotypic DST) were mainly used before 2017 (see Appendix 2). Specifically, sputum smear microscopy, culture testing, and risk assessment for drug-resistance were performed at the county level. Clinical isolates or sputum samples with positive results had to be transferred to the prefecture-level laboratory for DST before 2017. The rapid molecular DST was accessed in prefectures implementing international projects such as Zhenjiang, Lianyungang, and Nantong.

After the implementation of provincial comprehensive DR-TB control policies in all prefectures across Jiangsu in 2017, RMT on sputum samples can be performed at county level. Specifically, for counties equipped with Xpert MTB/RIF (Xpert, Cepheid, USA) (Zhenjiang and Nantong), RMT was performed on all TB cases while those equipped with Loop-mediated isothermal amplification (LAMP, Deaou Biotechnology, China) (Changzhou, Lianyungang, Huai'an, and Yangzhou), RMT was performed on TB cases with smear-negative results. Sputum samples and clinical isolates were transferred to the prefecture-level laboratory for DST since 2017. Charts showing the change in approach can be found in Appendix 2a-d.

### **4 Testing time**

Testing time is jointly influenced by the type of test used and the testing process. Rapid turnaround time for testing can bring timely treatment and reduce potential risk of spreading infection. We calculated the time required for the diagnosis of DR-TB (defined as days from the registration date in BMU to the confirmed date of DST). RMT has a significantly shorter time compared with solid culture and DST. From 2013 to 2019, the average time for RMT shortened by two thirds (from 18.86 to 6.36) while the average time for solid culture and DST dropped slightly, but still remains over 60 days (Fig. 2).

### **5 Percentage of pulmonary TB cases confirmed by bacteriology**

The percentage of pulmonary TB cases confirmed by bacteriology has increased from around 30% in 2013 to 55% in 2019. The application of various detection methods, such as culture and rapid TB testing resulted in the increase of the percentage of pulmonary TB cases confirmed by bacteriology (Fig. 3A-F). Prefectures that implemented international projects generally had better performance between 2013 and 2016. For instance, Zhenjiang, one site for Gates project between 2014 and 2016, had the highest percentage of pulmonary TB cases confirmed by bacteriology among the six selected prefectures. Most prefectures experienced significant improvement between 2017–2018 given the implementation of provincial-level policies in all prefectures (including the application of culture and RMT for suspected TB patients). The percentage of pulmonary TB cases confirmed by bacteriology in our six focus prefectures all reached 50% by 2019 while the disparities among prefectures gradually narrowed over the seven year time period reviewed (Table 2, Fig. 3A-F).

### **6 Percentage of bacteriologically confirmed TB patients tested for drug susceptibility**

In 2013, the percentage of bacteriologically confirmed TB patients tested for drug susceptibility varied from below 10% to over 90% across the prefectures. For prefectures that either performed DST on wider suspected DR-TB patients or perform DST before 2017, the

proportion of bacteriologically confirmed TB patients tested for drug susceptibility was higher. The proportion of bacteriologically confirmed TB patients tested for drug susceptibility has risen sharply, particularly among prefectures with low rates at the beginning since the implementation of provincial-level policies in 2017. In 2019, the percentage of bacteriologically confirmed TB patients tested for drug susceptibility was around 95% for all the prefectures (Table 2, Fig. 4A-F).

Table 2  
Testing results

Year	Percentage of pulmonary TB cases confirmed by bacteriology(%)							Percentage of bacteriologically confirmed TB patients tested for drug susceptibility(%)						
	2013	2014	2015	2016	2017	2018	2019	2013	2014	2015	2016	2017	2018	2019
Zhenjiang	31.2	39.2	39.0	40.2	45.5	55.2	56.0	89.0	89.8	86.1	84.8	100.0	95.9	97.0
Changzhou	32.4	29.8	31.4	32.2	32.6	51.1	58.2	91.4	88.6	83.0	84.9	100.0	91.5	96.9
Huai'an	25.1	26.3	30.6	31.9	36.4	43.7	51.9	8.2	8.7	9.5	25.5	53.4	98.3	99.6
Lianyungang	29.4	25.5	28.4	32.4	41.5	50.5	57.3	88.8	92.6	90.5	87.9	87.0	87.7	93.5
Nantong	27.0	26.7	25.4	38.2	30.1	51.3	55.3	94.5	76.1	73.7	96.3	57.4	95.7	97.6
Yangzhou	32.8	30.9	32.2	34.6	37.7	52.6	54.4	25.4	14.6	22.7	30.8	62.9	94.8	98.0

## 7 Influential factors for DRTB screening and detection

Factors associated with pulmonary TB cases confirmed by bacteriology were analyzed. Results showed that the application of RMT (Xpert) is 1.11 times ( $p < 0.01$ ) more likely to confirm TB cases than the smear test. The overall likelihood of pulmonary TB cases confirmed by bacteriology improved between 2013 and 2019. Females, the elderly (over 60), previously treated TB patients (compared with new patients), those with a cavity in a lung, and those residing outside the prefecture (compared with within county) are more likely to be bacteriologically confirmed. Patients are more likely to be bacteriologically confirmed by a county level diagnosis agency (compared with prefecture-level) and at general hospitals (compared with specialized hospitals, CDC, or TB dispensary).

We analyzed factors associated with bacteriologically confirmed cases tested for drug resistance. Results showed that the following types of patients were significantly more likely to be tested for drug resistance than patients with coverage of suspected high-risk DR-TB patients: patients with DST coverage of biologically confirmed TB cases (3.84 times), smear-positive TB patients (2.54 times), and smear-positive TB patients and smear-negative but culture-positive TB patients (2.30 times). Females, the elderly (over 60), previously patients treated (compared with new patients), and those residing within the county (compared with outside the county), were more likely to be tested for drug resistance. Bacteriologically confirmed cases were more likely to be tested by county level diagnosis agency (compared with prefecture-level) and at general hospitals (compared with specialized hospitals, CDC, or TB dispensary) for drug resistance.

Table 3

Influential factors for pulmonary TB cases confirmed by bacteriology and bacteriologically confirmed cases tested for drug resistance

	Model 1				Model 2			
	Y: TB cases confirmed by bacteriology				Y: Bacteriologically confirmed cases tested for drug resistance			
	B	S.E.	P value	Exp(B)	B	S.E.	P value	Exp(B)
Smear test as base								
Rapid molecular testing	0.107	0.027	0.000	1.113	/	/	/	/
DST coverage: suspected high-risk DR-TB patients as base								
Smear positive TB patients	/	/	/	/	0.931	0.042	0.000	2.537
Smear positive, smear negative but culture positive TB patients	/	/	/	/	0.834	0.042	0.000	2.304
Biologically confirmed TB patients	/	/	/	/	1.345	0.043	0.000	3.839
Year	0.174	0.005	0.000	1.190	0.196	0.009	0.000	1.217
Prefecture: Zhenjiang as base								
Changzhou	-0.139	0.032	0.000	0.870	-0.030	0.035	0.395	0.971
Huai'an	-0.273	0.035	0.000	0.761	-0.491	0.043	0.000	0.612
Lianyungang	0.014	0.042	0.734	1.014	0.016	0.051	0.759	1.016
Nantong	-0.312	0.027	0.000	0.732	-0.410	0.034	0.000	0.664
Yangzhou	-0.109	0.035	0.002	0.897	-0.212	0.044	0.000	0.809
Sex: male as base								
Female	0.144	0.017	0.000	1.155	0.248	0.021	0.000	1.281
Age group: over 60 as base								
Under45	-0.407	0.019	0.000	0.666	-0.335	0.022	0.000	0.715
45to60	-0.292	0.019	0.000	0.747	-0.250	0.022	0.000	0.779
Treatment: new as base								
retreatment	0.721	0.022	0.000	2.057	0.888	0.024	0.000	2.430
Cavitory disease: no as base								
Yes	0.078	0.037	0.034	1.081	0.052	0.041	0.206	1.053
Administrative level of diagnosis agency: county level as base								
Prefecture level	-0.087	0.029	0.003	0.916	-0.304	0.033	0.000	0.738
Type of current diagnosis agency: general hospitals as base								
Specialized hospitals	-0.092	0.024	0.000	0.912	-0.087	0.027	0.001	0.916
CDC or TB dispensary	-0.221	0.035	0.000	0.802	-0.247	0.043	0.000	0.781
Current residency: within county as base								
Within prefecture	0.001	0.025	0.965	1.001	-0.150	0.029	0.000	0.861
Within province	0.344	0.060	0.000	1.410	-0.456	0.082	0.000	0.634
Outside province	0.346	0.082	0.000	1.414	-0.214	0.102	0.036	0.808

	Model 1 Y: TB cases confirmed by bacteriology				Model 2 Y: Bacteriologically confirmed cases tested for drug resistance			
Constant	-1.074	0.057	0.000	0.342	-397.045	17.935	0.000	0.000
-2 Log likelihood	98704.781				77168.226			
Cox & Snell R Square	0.066				0.135			
Nagelkerke R Square	0.090				0.200			

## Discussion

Our study found that Jiangsu province has implemented a series of interventions to improve DR-TB control and prevention, such as workforce increases, the use of RMT devices, and allocation of special funds focused on DR-TB. With the application of RMT, the diagnostic process of DR-TB has become more convenient to patients with reduced testing time. The percentage of pulmonary TB cases confirmed by bacteriology has increased from around 30% in 2013 to over 50% in 2019, indicating that the implementation of new diagnostics, including RMT, have provided testing results more than the traditional smear microscopy. At the same time, the proportion of bacteriologically confirmed cases tested for drug resistance has increased substantially, indicating that the intervention of expanding the coverage of DST has reached more populations at risk of DR-TB.

Although there is no similar research analysing the impact of multiple DR-TB interventions on diagnosis, our findings are consistent with results from other evaluation studies on single DR-TB interventions, such as the implementation of RMT. For example, in Armenia the introduction of RMT increased the detection rate of RR-TB [17]; O. Oxlade et al found that the implementation of rapid DST at the moment of diagnosis was the most cost-effective strategy[18]; and a study in South Africa found that the implementation of molecular DST reduced the laboratory turnaround time from 55 days to 27 days[19]. These studies also found the same results as we did: the application of rapid DST has improved the diagnosis of DR-TB, and improved diagnosis is critical for achieving desired treatment results [20].

We observed that the three prefectures that participated in a Global Fund project and/or China-Gates project (Zhenjiang, Lianyungang, and Nantong) generally performed better than other prefectures, even after the partnerships concluded. This finding aligns with other studies. For example, in Nicaragua Plamondon et al also found that the presence of a Global Fund project improved TB control, built human resource capacity, and strengthened community involvement[21]. Our findings show that support from the Global Fund or BMGF had a strong emphasis on capacity building. Whether their support was for diagnostic devices or other best practices, such as DST to smear positive TB patients, the capacity building from international projects has had a long-lasting role in promoting the diagnosis for DR-TB [8].

Another significant finding is that the disparity in diagnosis for DR-TB among the six prefectures disappeared after 2017. This improvement can be attributed to the strong political commitment of the Jiangsu government in TB control and care. The provincial DR-TB intervention policies that were implemented were accompanied by sufficient resources including staff, funding, and diagnostic devices, which ensured the sound implementation of interventions. In addition to the infrastructure acquired from international projects, Jiangsu province made a significant investment to strengthen the infrastructure and capacity of laboratories of the prefectures that did not have international partnerships. For instance, both conventional equipment and RMT devices were introduced to all prefectures in Jiangsu (GeneChip to prefectures and LAMP to counties). In comparison, throughout the country only 44.2% of labs at the prefecture level and 27.5% at the county level have the same capacity as Jiangsu [22].

The diagnostic algorithm substantially improved after the application of RMT. The new process is more effective for the diagnosis of TB and DR-TB and reduces the testing time, enabling patients to receive more timely treatment. While the overall testing time was reduced, we noticed that in 2016, testing time for RMT (Hain or GeneChip) was slightly longer than previous year after its initial introduction to prefectures. This increase may reflect the learning curve of the lab staff to understand and execute the operating procedures. The average time for solid culture and DST continuously decreased after 2016, but it was still two times longer than the rapid molecular DST. Therefore, the application of the rapid molecular DST can reduce diagnosis delay and enable prompt treatment.

We observed significant changes across various indicators after the implementation of DR-TB detection interventions. The proportion of bacteriologically confirmed cases tested for drug resistance varied greatly across prefectures in 2013. Some prefectures, particularly

those with the least progress in DR-TB detection, experienced dramatic increases between 2016 and 2019 (Yangzhou and Huai'an). Not as international projects that only made progress in project sites, the implementation of provincial policies on DR-TB improved the DR-TB detection across all prefectures after 2017. However, most indicators assessed did not have a linear trend of improvement, indicating the complexity of policy interventions affected by other factors such as domestic migration and economic developments.

This is an observational study that used routine administrative data to reflect the effects of policy interventions across different regions at different time points between the window of 2013 and 2019. We attempted to capture the impact of a group of interventions that have been implemented in different combinations and sequences. Our study brought real-world evidence but also has some limitations. First, random control design was not possible since this study relied on routine, retrospective data. Second, we were only able to analyse indicators already collected by the TBIMS. Other factors impacting the results (i.e., the insurance status of TB patients) were not fully recognized or reflected in the analysis. Third, the data from TBIMS is designed for routine administration. It does not necessarily have robust quality assurance, and errors in data entry cannot be ruled out.

## Conclusion

We found international projects promoted local development in the detection of DR-TB, but the achievements has only been observed in project sites. To fully scale up DR-TB detection across the country, long-term sustainable policies at the provincial, or even the national level, are needed. The application of new diagnostic devices and expanded screening strategy have improved the detection of DR-TB patients. Along with these improvements in DR-TB detection, resources and commitment from local government have played an important role in improving the implementation of DR-TB detection.

## Abbreviations

BMGF: Bill & Melinda Gates Foundation

BMU: basic management unit

DR-TB: drug-resistant tuberculosis

DST: drug susceptibility testing

Global Fund: The Global Fund to Fight AIDS, Tuberculosis and Malaria

HIS: Hospital Information System

IA: Isothermal Amplification Technology

MDR-TB: multidrug-resistant tuberculosis

RMT: rapid molecular tests

RR-TB: rifampicin-resistant tuberculosis

TB: tuberculosis

TBIMS: TB Information Management System

## Declarations

### Ethics approval and consent to participate

We performed analysis on routine administrative data and no ethical approval was required.

### Consent for publication

We performed analysis on routine administrative data, consent for publication is not applicable.

# Availability of data and materials

The datasets analysed during the current study are not publicly available due the regulation on TBIMS but are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests

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## Authors' contributions

ST, XD, WM, WL and LZ conceptualized the paper. XD, WM, HY, QL, PL, HJ, XZ, FL, JX, CZ, WJ, LG and JH analysed and interpreted the data and draft the manuscript. ST and LZ also contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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## References

1. Rubin and Rita, *Profile: Institute for Health Metrics and Evaluation, WA, USA*. Lancet, 2017. **389**(10068): p. 493.
2. Uplekar, M., et al., *WHO's new end TB strategy*. Lancet, 2015. **385**(9979): p. 1799-1801.
3. Wang, L., et al., *Tuberculosis prevalence in China, 1990–2010; a longitudinal analysis of national survey data*. The Lancet, 2014. **383**(9934): p. 2057-2064.
4. Zhao, Y., et al., *National Survey of Drug-Resistant Tuberculosis in China – NEJM*. N Engl J Med, 2012. **366**(23): p. 2161-2170.
5. Wells, C.D., *Picking up the pace-scale-up of MDR tuberculosis treatment programs*. New England Journal of Medicine, 2010. **363**(19): p. 1781-4.
6. Annabel, B., D. Anna, and M. Hannah, *Global tuberculosis report 2019*. Geneva: World Health Organization, 2019.
7. Wang, L., 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**(6): p. e0177536.
8. Li, R., et al., *Effect of a comprehensive programme to provide universal access to care for sputum-smear-positive multidrug-resistant tuberculosis in China: a before-and-after study*. The Lancet Global Health, 2015. **3**(4): p. e217-e228.
9. Long, Q., Y. Qu, and H. Lucas, *Drug-resistant tuberculosis control in China: progress and challenges*. Infectious Diseases of Poverty, 2016. **5**(1): p. 9.
10. Medicine, I.O., *The Global Crisis of Drug-Resistant Tuberculosis and the Leadership of the BRICS Countries: Challenges and Opportunities*. 2014.
11. Huang, F., et al., *Added Value of Comprehensive Program to Provide Universal Access to Care for Sputum Smear-Negative Drug-Resistant Tuberculosis, China*. Emerging Infectious Diseases, 2019. **25**(7): p. 1289-1296.
12. Huang, F., et al., *Electronic recording and reporting system for tuberculosis in China: experience and opportunities*. Journal of the American Medical Informatics Association Jamia, 2013. **21**(5): p. 938-941.
13. *High-quality health systems in the Sustainable Development Goals era: time for a revolution*. Lancet Global Health, 2018.
14. Tao, et al., *Under-reporting of diagnosed tuberculosis to the national surveillance system in China: an inventory study in nine counties in 2015*. Bmj Open, 2019.

15. Wang, N., et al., *Using electronic medication monitoring to guide differential management of tuberculosis patients at the community level in China*. BMC Infectious Diseases, 2019. **19**(1): p. 844.
16. Access to and affordability of healthcare for TB patients in China: issues and challenges. Infectious Diseases of Poverty, 2016. **5**(1): p. 10.
17. Kabasakalyan, E., et al., *Change in TB diagnostic profile after introduction of GeneXpert MTB/RIF assay in National TB Program of Armenia, 2013-2017*. Journal of Infection in Developing Countries, 2019. **13**(5.1): p. 022S-027S.
18. Oxlade, O., D. Falzon, and D. Menzies, *The impact and cost-effectiveness of strategies to detect drug-resistant tuberculosis*. European Respiratory Journal, 2012. **39**(3): p. 626-34.
19. Warren, R.M., *Implementation of new tools for multidrug-resistant tuberculosis detection and control*. International Journal of Mycobacteriology, 2016. **5**: p. S67.
20. de Vries, G., et al., *Health system factors influencing management of multidrug-resistant tuberculosis in four European Union countries-learning from country experiences*. BMC public health, 2017. **17**(1): p. 334.
21. Plamondon, K.M., L. Hanson, and R.L. Abonyi, *The Global Fund and Tuberculosis in Nicaragua*. Canadian Journal of Public Health, 2008.
22. Li, X., et al., *Analysis of tuberculosis laboratory capacity building in China from 2011 to 2015*. Chin. J of PHM, 2019. **035**(4): p. 441-444.

## Table

Table 1 not available with this version.

## Figures

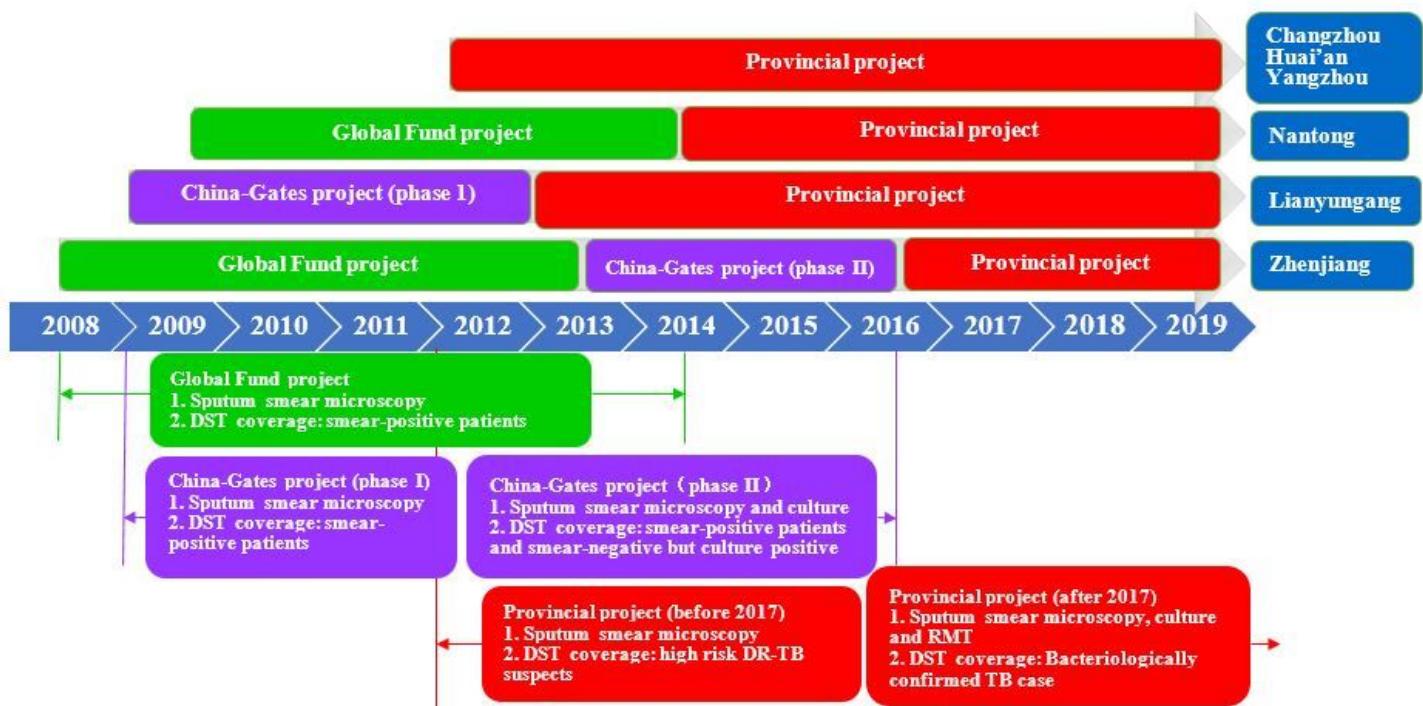
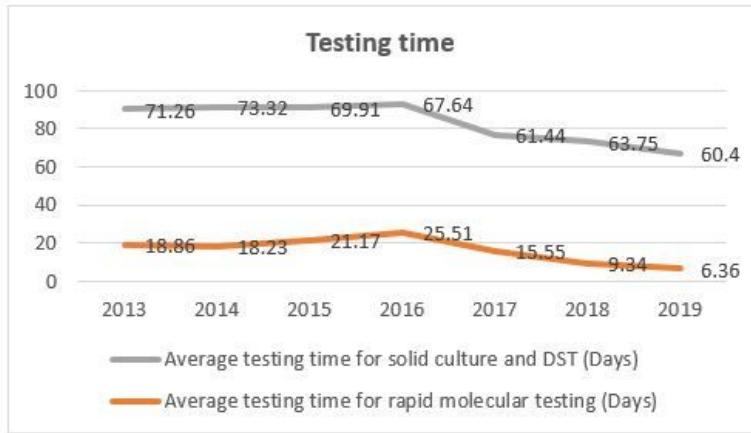


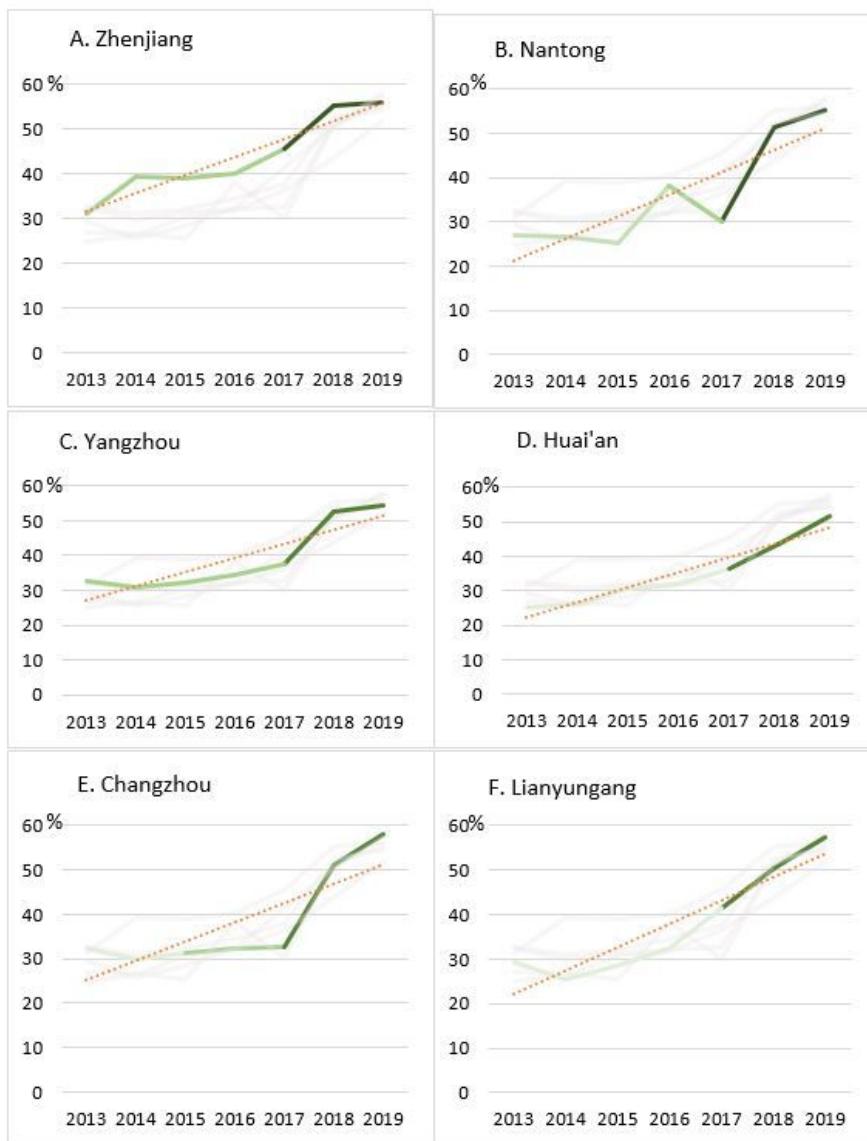
Figure 1

Timeline of major policies and interventions on the screening and diagnosis of DR-TB in Jiangsu, 2008-2019



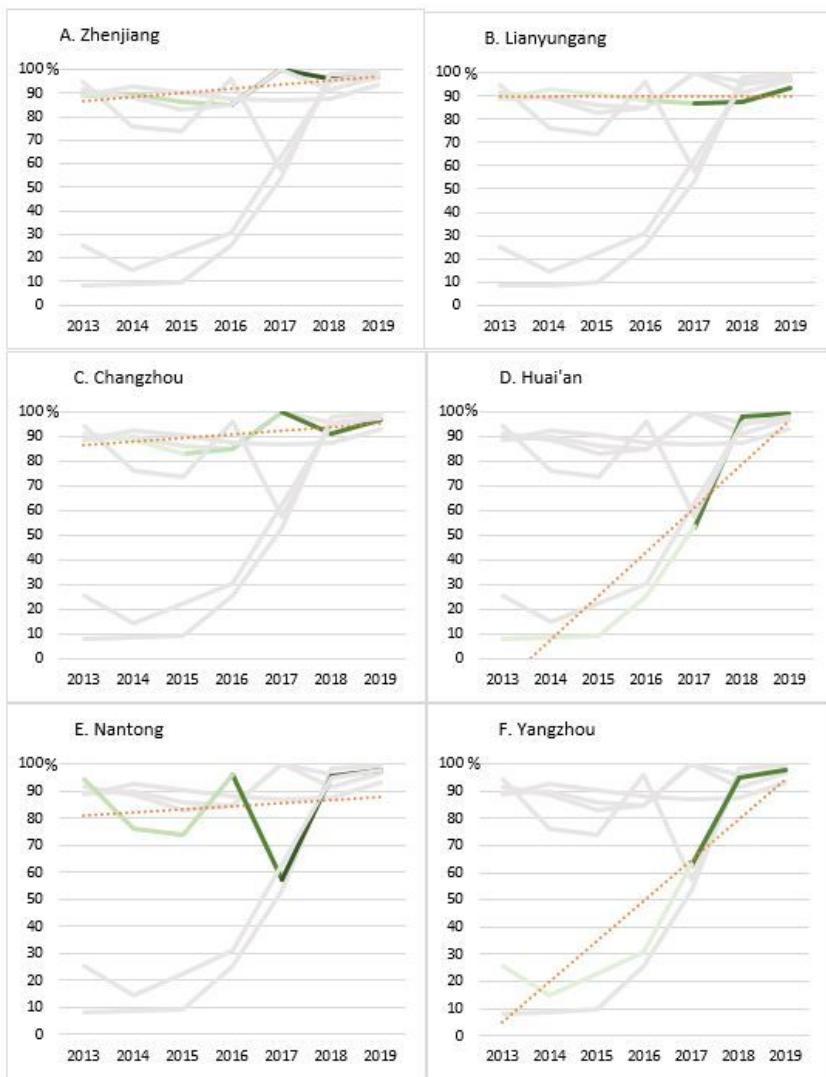
**Figure 2**

Average Testing time (Days)



**Figure 3**

A-F Percentage of pulmonary TB cases confirmed by bacteriology \*Green line: Percentage of pulmonary TB cases confirmed by bacteriology in selected prefecture Darker green means more interventions Grey line: Percentage of pulmonary TB cases confirmed by bacteriology in the other five prefectures Red line: trend line



**Figure 4**

A-F Percentage of bacteriologically confirmed TB patients tested for drug susceptibility

## Supplementary Files

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- APPENDIX.docx