Research paper

The impact of the COVID-19 epidemic on tuberculosis control in China

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A B S T R A C T

Background: In response to the COVID-19 epidemic, China implemented a series of interventions that impacted tuberculosis (TB) control in the country.

Methods: Based on routine surveillance data and questionnaires, the study analyzed TB notification, follow-up examinations, and treatment outcomes. The data were split into three phases in relation to outbreak, lockdown and reopen when the nationwide COVID-19 response started in 2020: control (11 weeks prior), intensive (11 weeks during and immediately after), and regular (4 additional weeks). Data from 2017–2019 were used as baseline.

Findings: The notified number of TB patients decreased sharply in the 1st week of the intensive period but took significantly longer to rebound in 2020 compared with baseline. The percentages of TB patients undergoing sputum examination within one week after 2 months treatment and full treatment course in the intensive period were most affected and decreased by 8% in comparison with control period. 75-2% (221/294) of counties reallocated CDC and primary health care workers to fight the COVID-19 epidemic, 26-9% (725/2694) of TB patients had postponed or missed their follow-up examinations due to travel restrictions and fear of contracting COVID-19.

Interpretation: In the short term, the COVID-19 epidemic mostly affected TB notification and follow-up examinations in China, which may lead to a surge of demand for TB services in the near future. To cope with this future challenge, an emergency response mechanism for TB should be established.

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Research in context

Evidence before this study

We searched PubMed, and two preprint servers (bioRxiv and medRxiv) for articles describing the impact of COVID-19 on TB control with key words “COVID-19 or SARS-CoV-2 or 2019-nCoV or novel coronavirus” and “tuberculosis” up to May 29, 2020. Some studies have discussed, anticipated, or modelled the possible impact of COVID-19 on TB control, some studies only focus on one aspect of impact on TB testing, notification, or clinical course of TB patients co-infected with COVID-19. There were no studies that fully described the impact on TB notification, follow-up examinations, and treatment outcomes with detailed data, and the impact remains unclear.

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1. Introduction

As of August 11, 2020, the number of people who have died from the novel coronavirus disease 2019 (COVID-19) since January reached 728,013 of 19,718,030 confirmed cases, reported from 216 countries/regions globally [1]. Noting the high morbidity and mortality rates from the disease and its characteristics of high transmission, Li et al. [2-5] more and more countries began to mobilize and dedicate a large amount of public health resources to fight the epidemic, including the suspension or reduction of outpatient and inpatient services, reallocation of medical staff to COVID-19, and reinforcement of laboratory testing [1]. This has affected the resolution of other public health issues that deserve the public’s concern and should be addressed [6,7]. In China, most of hospitals received COVID-19 cases used to be TB designated hospitals, responsible for tuberculosis (TB) diagnosis and treatment. We assessed the effects of COVID-19 epidemic on TB control in China, including the reduction in cases for the intensive intervention period of 76 days of lockdown and afterwards, as well as follow-up examinations and treatment outcomes.

TB, like COVID-19, is an airborne transmitted infectious disease. It is the leading infectious disease killer globally, surpassing HIV/AIDS and malaria, with 10 million new cases and 1.5 million deaths estimated in 2019 [8]. In response to the global TB epidemic, the United Nations Sustainable Development Goal proposes the target of End TB by 2030 [9]. Despite the sheer numbers globally, TB remains overshadowed by HIV and malaria and currently the COVID-19 epidemic [10], and the impact of COVID-19 on TB outcomes is of serious concern [11]. The current studies either modeled the potential impact of COVID-19 on TB control under different scenarios based on assumptions without hard data as input [12-14], or only focused on the impact of COVID-19 on TB notification or testing [15-17], and there is no study fully discussing the short-term impact on TB notification, follow-up examination and treatment outcomes with real data of country emerged from this crisis.

At the very beginning of the COVID-19 outbreak in China, the government implemented a series of multifaceted public health interventions and enforced them strictly throughout the country. These included the cancellation of all public gatherings, the prohibition of all public gatherings, and the requirement for all residents to stay at home. These interventions proved successful in mitigating the spread of COVID-19 [18-20]. However, these measures could have a potential impact on TB control in China. On one hand, these measures may limit people's seeking medical behavior and the provision of health care services in hospitals. On the other hand, the measures will reduce the transmission of TB occurring outside the household. As a country with a high TB burden, China has placed great emphasis on TB control and achieved substantial progress over the past decades [21], but TB remains a major public health issue in the country. The government issued a three-year action plan to stop TB in 2019 [22]. To successfully achieve these goals and the ultimate target of End TB, it is critical for China to address the impact of the COVID-19 epidemic on TB control and develop effective solutions to be used in China and potentially use for reference by other countries.

2. Methods

2.1. Sources of data

This study used two sources of data: routine national surveillance data and questionnaires.

Routine national surveillance data: Medical records of TB patients from 2017 to 2020 were extracted from the national TB Information Management System (TBIMS) on May 29, 2020, including demographic characteristics (e.g., age, sex, and address), diagnosis information (e.g., date of first symptom onset, date of first seeking medical care, and diagnosis result), and follow-up examinations and treatment outcomes (e.g., date and result of sputum smear after 2 month treatment and full treatment course, the reason to stop treatment). All information was entered into the TBIMS via the internet by medical staff from authorized hospitals for TB diagnosis and treatment (i.e., “TB-designated hospital”) by the local health administration [23].

Questionnaires: Chinese Tuberculosis control network is composed of the Centers for Disease Control and Prevention (CDC), TB-designated hospitals, and primary health care units (PHCs) at each county [24]. Among them, 294 counties (10% of all counties) were randomly selected by province, and questionnaire survey was conducted to all of them, which include 2 counties from Wuhan city and 8 counties from the other cities of Hubei province. Health facilities were requested to answer the questions about daily operation of the TB outpatient clinic and hospitalization, laboratory testing work, medical staff reassignment to COVID-19 units, anti-TB drug supply, traffic restrictions within and beyond the county, and suggestions for next steps. About eighteen TB patients per county were also surveyed for a sample size of 4257. These patients were interviewed by local CDC workers via telephone regarding follow-up examinations, treatment adherence, and similar matters.

2.2. Key time points and periods

To better understand the potential impact of COVID-19 on TB control in China, this study used three periods based on two key time points: January 25, 2020 (The nationwide COVID-19 response started), and April 8, 2020 (Wuhan reopened). Eleven weeks before January 24, 2020, was considered as the control phase without any interventions for COVID-19. The second period of 11 weeks, from January 25, 2020, to April 8, 2020, was considered as the intensive phase due to the COVID-19 epidemic. The final phase of 4 weeks began on April 9, 2020, with regular interventions for the epidemic. The three years prior to the epidemic, 2017–2019, were used as the baseline and were split into 3 counterpart periods by date (Fig. 1).

In the intensive period, all people were supposed to stay at home due to containment measures in response to the COVID-19
epidemic. These measures included traffic restrictions, social distancing, and home confinement. In China most TB-designated hospitals were appointed as COVID-19 hospitals. Similarly, the medical staff, especially in the laboratories, were reassigned to fight against COVID-19, and certain areas, such as TB outpatient clinics, were directly closed.

On April 8, 2020, China lifted the 76-day lockdown on Wuhan city where the outbreak of the COVID-19 crisis started in China. The reopening of Wuhan city meant the whole country could begin to resume work and normal life in an orderly fashion.

In summary, three time periods were classified to better understand and compare the impact of the COVID-19 epidemic on TB control in China. Firstly, there was no impact on TB control during the COVID-19 epidemic in the control phase. Secondly, there was major influence from COVID-19 in intensive phase. Thirdly, there was moderate impact on TB control in the regular phase.

The Spring Festival is an important holiday in China, beginning on Chinese New Year's Eve and lasting for seven days. During this one-week national vacation, most people in China avoid seeking medical care and instead reunite with family. Yet in 2020, the Central government decided to form a Leading Group and start the nationwide COVID-19 emergency response on January 25, which was also at the beginning of one-week national holiday. Thus we selected the time point of Chinese New Year of 2017-2019 and eleven weeks before and 15 weeks after the time point as baseline.

2.3. Statistical analysis

TB notification breakdown by weeks, as well as the percentage of laboratory confirmed and migrant cases, were calculated to address the possible difference. Patient delay (from date of symptom onset to date of seeking medical care), diagnosis delay (from date of seeking medical care to date of confirmed diagnosis), and treatment delay (from date of confirmed diagnosis to date of initiating therapy) were compared by 3 periods (before, during and after Chinese Spring Festival) during 2017–2020 to reflect any changes from the impact of COVID-19 outbreak.

In China, all TB patients are requested to have sputum smear microscopy examination after 2 months treatment, as well as after the full treatment course. If the follow-up sputum smear microscopy examinations are in 7 days overdue, it will be calculated as none of show-up for following-up. The sputum conversion rate after 2 months treatment and cured rate for smear positive patients were calculated to evaluate the treatment outcomes.

Cochran-Armitage Trend Test were used for categorical data, and Kruskal-Wallis Test was used for continual data. All statistical tests were two-tailed, and the p value <0.05 was considered significant. All the tests were done by Base R (version 3.6.3).

2.4. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. 2020 COVID-19 periods

The TB case numbers notified in the control, intensive, and regular periods of 2020 from routine national surveillance data were 129782, 103230, and 52922 respectively (Fig. 1). The percentage of laboratory confirmed cases decreased from 53% in the control period to 50-8% in the regular period, and the percentage of mi-
grant cases declined from 29-3% in the control period to 25-3% in the intensive period (Table 1).

The median (interquartile range, IQR) of patient delay in the control, intensive and regular periods of 2020 were 18(8–34), 19(7–36) and 18(8–34) days respectively. The median (IQR) of diagnosis delay in the control, intensive and regular periods were 1(0–6), 0(0–5) and 1(0–5) days respectively.

In 2020, the percentage of TB patients who had a sputum examination within one week after 2 months treatment decreased from 68-8% in the control period to 60-2% in the intensive period, the percentage of sputum examination within one week after the full treatment course declined from 54-6% in the control period to 46-4% in the intensive period. The sputum conversion rates after 2 months treatment for smear positive patients who had sputum examination in the control, intensive, and regular periods of 2020 were 93-1%, 93-6%, and 91-9% respectively. The cured rates for smear positive patients who had sputum examination after full treatment course in the control, intensive, and regular periods were 85-1%, 84-7%, and 84-7% respectively (Table 1).

### Table 1

| Notification                        | Control                          | Intensive                        | Regular                          | p value   |
|-------------------------------------|----------------------------------|----------------------------------|----------------------------------|-----------|
| Laboratory confirmed cases (%)      | 68996/129782 (53-2%)             | 52935/103230 (51-3%)             | 26898/52922 (50-8%)              | <0.0001   |
| Migrant cases (%)                   | 38072/129782 (29-3%)             | 26136/103320 (29-3%)             | 13611/52922 (25-7%)              | <0.0001   |
| Follow-up examination               |                                  |                                  |                                  |           |
| Sputum examination after 2 months   | 94198/136963 (68-8%)             | 70183/116509 (60-2%)             | 20684/31917 (64-8%)              | <0.0001   |
| treatment (%)                       | 97274/178314 (54-6%)             | 67264/144984 (46-4%)             | 26311/52892 (49-7%)              | <0.0001   |
| Treatment outcome of smear positive |                                  |                                  |                                  |           |
| Sputum conversion rate after 2 months treatment (%) | 41716/44816 (93-1%)      | 33165/35423 (93-6%)              | 8771/9548 (91-9%)                | 0.7475    |
| Cured rate (%)                      | 44252/51998 (85-1%)              | 33862/39992 (84-7%)              | 10997/12988 (84-7%)              | 0.6159    |

In the three years prior to COVID-19, the average notification of TB patients decreased sharply from 13,697 to 3202 in the 1st week after the Chinese Spring Festival and then quickly rebounded to the previous level from 3202 to 16,562 in the 2nd week of the three years. However, in 2020 it took about 10 weeks to return to the previous level (Fig. 2). The percentages of laboratory confirmed cases in 2017–2019 increased from period 1 to period 3 (Fig. 3, Table 2). On the contrary, the percentages continuously decreased from control period to regular period in 2020. The percentages of migrant cases increased from period 1 to period 3 in 2018–2019 (Fig. 4, Table 2), while the percentage in the intensive period of 2020 was the lowest among the three periods.

The patient delays in the three periods of 2017–2019 were similar to that in 2020, first increased and then decreased (Fig. 5). There was no significant difference in diagnosis delay between period 1 and period 2 of 2018–2019, which was different from that of 2020 (Fig. 6). The median (IQR) of treatment delay for all three periods of 2017–2019 were all 0(0-0) days, the same as in 2020.
There were no significant differences for the percentage of sputum examination within 7 days after 2 months treatment and full treatment course among the three phases of 2018-2019 (Figs. 7-8, Table 3), while the percentages in the intensive period of 2020 were the lowest. The sputum conversion rate after 2 months treatment for smear positive patients who had sputum examination was no significant difference among the three phases of 2017-2019, which were similar to that of 2020. The cured rate for smear positive patients who had sputum examination at the end of prescribed treatment course had a totally same trend as the sputum conversion rate after 2 months treatment (Figs. 9–10, Table 4).

### 3.3. Questionnaire results about the impact of COVID-19 on TB control

From the perspective of health providers, the survey results indicated that 75.2% (221/294) of counties reallocated CDC and primary health care workers to fight the COVID-19 epidemic, and 37.8% (111/294) of counties sent the TB laboratory staff to work for COVID-19 testing. 14.6% (43/294) and 13.6% (40/294) of counties were temporarily closed TB outpatient clinics and TB laboratory respectively during the intensive period. 4.4% (13/294) of counties faced a shortage of laboratory reagents for TB, and 8.2% (24/294) of counties experienced a shortage of anti-TB drug during the epidemic.

The survey indicated that TB cases could not easily access to health facilities, due to 84.6% (247/294) and 71.1% (209/294) of counties applied strict intra-county and inter-city travel restrictions. 26.9% (725/2694) of TB patients had postponed or missed going for their follow-up examinations, due to travel restrictions and fear of contracting COVID-19.

### 4. Discussion

Two previous studies showed that TB is a seasonal disease in China with a predominant spring peak based on monthly notification data [25,26], however, they did not reveal the reason behind the phenomena. In our study, the weekly notification data indi-
Fig. 4. The percentage of migrant TB cases in 11 weeks before and 15 weeks after the Chinese Spring Festival, 2017–2020 in China. Migrant cases: The patient’s current residence address and household registration do not belong to the same county (patient floats to the place rather than his/her origins).

Fig. 5. TB patient delay in China breakdown by three time periods, 2017–2020. Patient delay: from date of first symptom onset to date of first seeking medical care. Boxplot was used for describing the distribution of delay along y axis, the junction of different colors in the box was median. p value: Kruskal-Wallis Test, p value <0.05 is considered significant.

cated a sharp drop immediately after the Chinese Spring Festival and a spike soon afterwards, which could explain the spring peak. During the weeklong Spring Festival holiday, most people staying at home with their families, the medical care–seeking behavior of presumptive TB is greatly influenced. Meanwhile, the TB outpatient clinics of many designated hospitals are closed during this time.

However, the trend in 2020 was quite different from that of 2017–2019: the speed of bouncing back to the previous level was much slower than that in previous years, which could be caused by nationwide COVID-19 interventions. The change was similar to other studies based China’s provincial surveillance data [27,28]. There are two possible explanations: (1) TB service delivery system disruptions. The presumptive TB tracing and referral was stopped due to the reallocation workers of CDCs and PHCs to fight the COVID-19 epidemic among 75–2% of counties. 14–6% of counties couldn’t provide clinical service as they temporarily closed TB
outpatient clinics during the intensive period. (2) Lack of access. Due to the majority of counties applied strict inter-city and intra-county travel restriction, presumptive TB had difficulties in visiting health facilities and seeking medical care.

The gold standard for TB diagnosis is to find *Mycobacterium tuberculosis* in patient clinical samples that include sputum or other specimen [29]. The “13th Five-Year Plan” of the National TB Control Program issued by the Chinese government requires strengthening laboratory construction and ramping up use of molecular biology equipment all over the country to increase the percentage of bacteriologically confirmed TB patients to not less than 50% by 2020 [30]. From 2017 to 2019, this indicator rose gradually significant, which was either indicated the progress of TB control program in China, or likely due to the large sample sizes [31]. By the end of 2019 (the control period of 2020), the percentage had exceeded 50%, but it fell off below 50% after the holiday, which was caused by reduced laboratory capacity, e.g., TB laboratory was closed, TB laboratory staff was transferred for COVID-19 testing, and a short-
Fig. 8. The percentage of sputum examination within 7 days after the full treatment course in the period of 11 weeks before and 15 weeks after the Chinese Spring Festival, 2017–2020.

Table 3
Sputum examination within 7 days after 2 months treatment and full treatment course in China, 2017–2020.

| Year | Period | Examination after 2 months treatment n (%) | Examination after full treatment course n (%) | p value |
|------|--------|--------------------------------------------|---------------------------------------------|---------|
|      |        | p value                                   |                                             |         |
| 2017 |        |                                            |                                             |         |
|      |        | <0.0001                                   | <0.0001                                     |         |
|      |        |                                            |                                             |         |
| 2018 |        |                                            |                                             |         |
|      |        | 0.4838                                    |                                             |         |
|      |        |                                            |                                             |         |
| 2019 |        |                                            |                                             |         |
|      |        | 0.1383                                    |                                             |         |
|      |        |                                            |                                             |         |
| 2020 |        |                                            |                                             |         |
|      |        | <0.0001                                   |                                             |         |

Table 4
Treatment outcome among smear positive TB patients in China, 2017–2020.

| Year | Period | Sputum conversion rate after 2 months treatment n (%) | Cured rate n (%) | p value |
|------|--------|--------------------------------------------------------|-----------------|---------|
|      |        | p value                                               |                 |         |
| 2017 |        | 0.3277                                                | 0.9080          |         |
|      |        | 0.1602                                                | 0.2300          |         |
|      |        | 0.1917                                                | 0.2022          |         |
|      |        | 0.7475                                                | 0.6159          |         |

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age of laboratory reagents for TB occurred. In addition, the strict inter-city travel ban adopted by the majority of counties led to decline the number of migrant population, the same as migrant TB patients.

The change trend of diagnosis delay in 2020 was different from the other three years. As some symptoms of TB are similar to COVID-19, the presumptive TB will be treated in priority and diagnosed quickly during the epidemic. In China, all diagnosed TB in the designated hospital will be provided with free anti-TB drug and that’s why there were no changes for treatment delay. However, due to the absence of presumptive TB from visiting hospital during the pandemic, the possibly prolonged patients delay remains unknown and needs further monitoring.

In terms of follow-up examinations, there was a clear slump in the intensive period for sputum examination after both two months treatment and full treatment course. This was due to several factors. First, as mentioned above, many counties transferred their TB laboratory to COVID-19 testing and temporarily closed their TB outpatient clinic during the intensive period, leaving TB patients with nowhere to go for sputum examination. Second,
some TB patients had postponed or missed their sputum examination in fear of infection with COVID-19 [32], which was similar to the impact of Ebola on TB control [33].

Although a few counties experienced shortage of anti-TB drug during the epidemic, health care workers tried their best to solve the problem and deliver the drugs to patients. Almost all primary health care units were unable to visit TB patients as required to ensure regular medication and treatment adherence, thus TB patients used self-administered therapy or directly observed therapy (DOT) by family members. However, there was no significant difference among the sputum conversion rate of smear positive patients after 2 months treatment in the three periods, as well as the cured rate. This is consistent with previous studies that DOT improves neither TB treatment completion and cured rate nor microbiologic failure and relapse, when it was compared to self-administered therapy [34–36]. Other studies, however, show a decline in relapse rates with DOT [37,38]. As some patients didn’t visit the TB clinic during the epidemic and the treatment outcomes remain unknown, our study only evaluated TB patients who visited the TB clinic. The long-term impact of COVID-19 on treatment adherence, cure rates, incidence and mortality in China still need to be further studied.

5. Conclusion

The impact of COVID-19 on TB control in China can be examined from two sides. Patients were either unable to access medical services due to closures and travel restrictions or hesitated due to concerns about infection with COVID-19. It might be a positive impact on less transmission occurring outside the household and negative impact on more transmission within the household during the lockdown phase. Meanwhile, health service providers working in TB experienced lack of both human resources and laboratory capacity. In the aftermath of the epidemic, there will likely be pent-up demand for TB services, for which it is necessary to prepare. To cope with this future challenge, an emergency response mechanism should be established, including increased human resources, scale up of laboratory testing, active case finding activities, household contact management, enhanced anti-TB drug delivery, and other measures as needed to ensure timely TB diagnosis and treatment for all those who need it.

5.1. Limitations

This study was subject to a few limitations. First, since the timing of the response to COVID-19 was not exactly the same across the country, and the control measures varied by region, the impact on TB control may also differ. This study did not attempt to quantitatively analyze this effect. Second, staying at home during the epidemic may have led to increased close contact among family members of TB patients. Health service disruption may lead to increased TB incidence and mortality. The long-term impact of COVID-19 on TB control, which needs further study, will surface beyond the time frame of this study and cannot be evaluated in this paper. Third, given that the incidence of multidrug-resistant TB (MDR-TB) is not high in China, and the number of MDR-TB patients is not large, this study did not analyze the specific impact of the COVID-19 outbreak on MDR-TB diagnosis and control.

Declaration of Competing Interest

The authors have no competing interests.

CRediT authorship contribution statement

Huang Fei: Conceptualization, Visualization, Formal analysis, Writing - original draft. Xia Yinyin: Conceptualization, Visualization, Formal analysis, Writing - original draft. Chen Hui: Conceptualization, Data curation, Writing - original draft. Wang Ni: Conceptualization, Data curation, Writing - original draft. Du Xin: Conceptualization, Data curation. Chen Wei: Conceptualization, Data curation. Li Tao: Conceptualization, Data curation, Writing - original draft. Huan Shitong: Conceptualization, Data curation. Sun Miaomiao: Conceptualization, Data curation, Writing - original draft. Chen Mingting: Conceptualization, Data curation. Salmaan Keeshavjee: Conceptualization, Visualization, Supervision. Zhao Yanlin: Conceptualization, Visualization, Writing - original draft, Supervision. Daniel P. Chin: Conceptualization, Visualization, Supervision. Liu Jianjun: Conceptualization, Supervision.

Data sharing

Data sharing requests will be considered by China CDC upon written request to the corresponding author. Aggregated patient data will be available subject to a written proposal and a signed data sharing agreement.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jlanwpc.2020.100032.

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