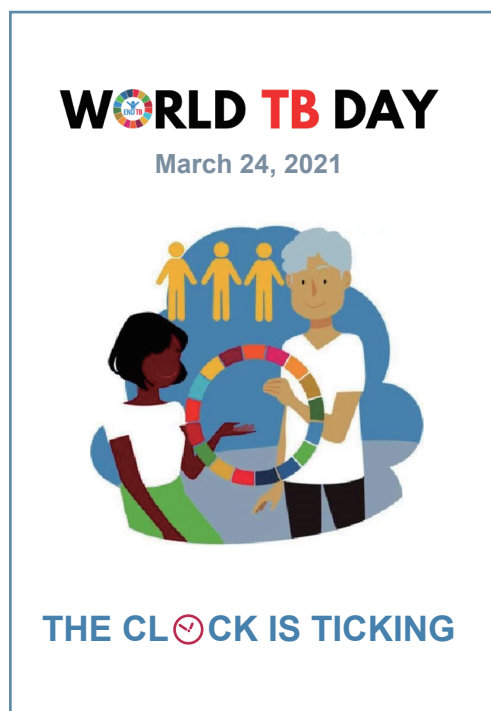


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THE WORLD TB DAY ISSUE

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Foreword

Facing the Challenge of Tuberculosis: Towards “End TB in China by 2035”

“The Clock is Ticking” is the theme of 2021 World Tuberculosis (TB) Day. Each year, we recognize on March 24 the important date in 1882 when the German scientist Dr. Robert Koch announced his discovery of the causes of tuberculosis, that is *Mycobacterium tuberculosis*, which has caused billions of the death in the past. The fight against TB, one of the threats to global public health, needs to be people-oriented, follow sustainable development principles, and encourage knowledge sharing and policy exchange in the world that was endorsed by the World Health Organization’s (WHO) End-TB Strategy (1–2). In addition, the United Nation (UN) leader’s summit call for further emphasis on TB control and prevention urged the global community to provide treatment to all those with TB in developing countries, to reduce the threat to global public health, and to reduce the economical and labor losses caused by TB (3). World TB Day raises awareness of the challenges that hinder our progress toward the elimination of this devastating disease.

TB is a global disease. In China, TB has been put into category II notifiable disease since 1996. A systematic TB control and prevention program had been launched in the 1990s and has been supported by national effort and prioritization. As a result, TB prevalence in China was halved between 1990 and 2010, mortality rates fell by almost 80%, and incidence rates fell 3.4% per year (4). Despite these achievements, China continues to have one of the highest TB burdens in the world, ranking number 3 in the world in several TB burden indicators.

POLITICAL COMMITMENT

The Chinese government has been paying close attention to TB control and prevention as the State Council has issued a series of “5-year national TB control programs” (11th, 12th, and 13th) to strengthen the TB control and prevention nationwide and to increase funding for scientific research in terms of diagnostics, digital health, new drugs, new vaccines, and implemental and operational research (5–7). Chinese scientists and specialists continue to carry on investigative studies to understand the burden of TB, the characteristics of the predominant strains (8–10), the effectiveness of infection control measures, means of assisting vulnerable populations, novel drug therapies, and technology to support community case management using mobile phones and medical monitors. The scientific community continues to recognize that TB is impeding the further progress and fulfillment of Healthy China 2030.

Recently, China has established a series of policies and several major measures in its healthcare system, actively and effectively slowed the TB epidemic, and reduced the number of new TB cases by over 300,000 when compared to projections. These are major achievements in TB control and prevention that have had high socioeconomic effectiveness. The central government provided financial support of approximately 1.2 billion CNY for TB control and prevention every year, and local governments and health insurances supplement this figure.

COMPREHENSIVE TB CONTROL AND PREVENTION STRATEGY

The National TB Program (NTP) is committed to strengthening research on strategies and measures for TB control and prevention; organizing and implementing action plans; conducting scientific research on applying these techniques; providing technical guidance, staff training and quality control for disease control and prevention and public health services throughout the country; and acting as the national technical leading work group for TB prevention and control (Figure 1).

To address these challenges, scientific research and innovation are key to controlling and ultimately eliminating this disease. Innovations in TB control efforts have embraced new tools and approaches to prevent, diagnose, and treat TB and drug-resistant TB (11–15). However, the research is continuous and treating TB depends on

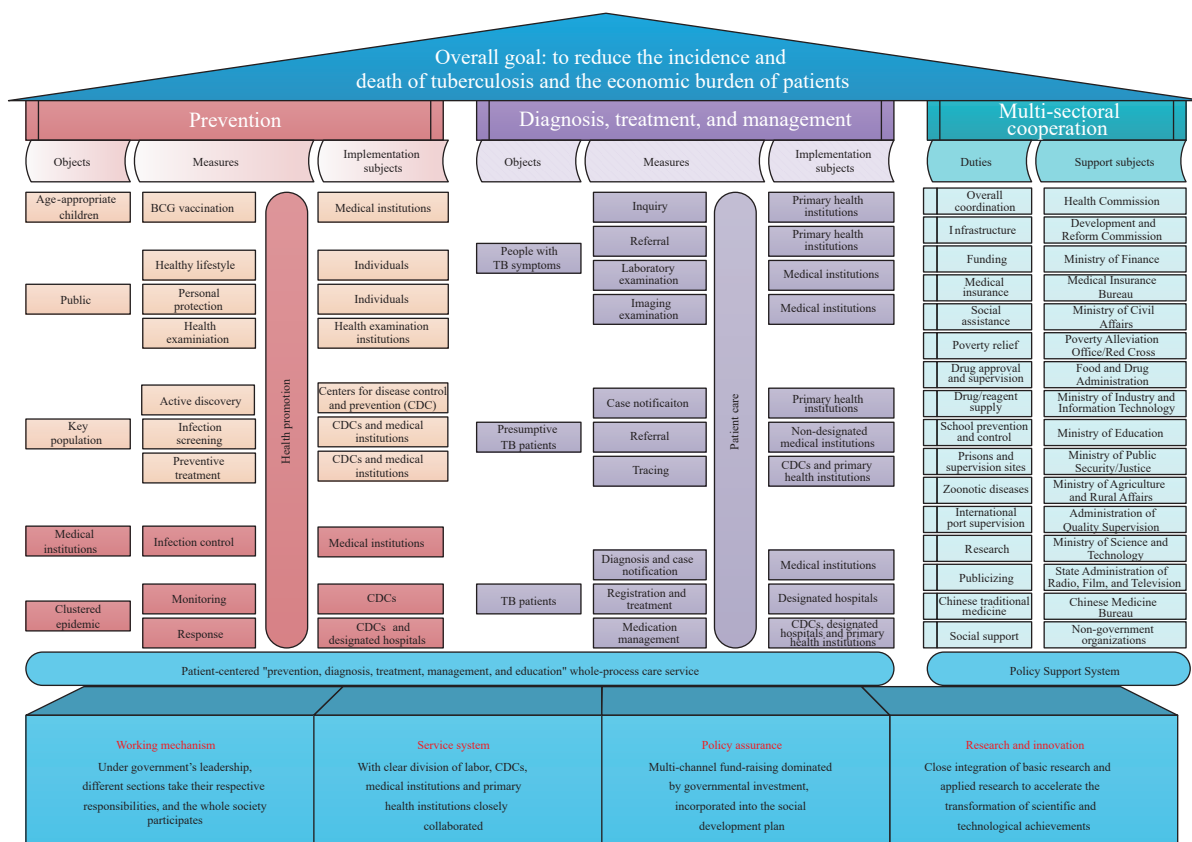


FIGURE 1. Tuberculosis control and prevention strategy in China.

multidisciplinary and multisectoral collaboration across the country because the problems are complex and multifaceted and cannot be solved simply. Therefore, international and domestic scientists and stakeholders must collaborate in research and development of new vaccines and new anti-TB drugs.

TUBERCULOSIS CONTROL AND PREVENTION KEY MEASURES

TB is a major priority due to the costs and challenges it brings to the basic public health service system, hierarchical medical system, family doctor signing system, and payment of medical costs by categorizing cases (based on diagnosis-related groups, DRGs). These challenges must be overcome by improving service at the county and township levels by further reforming the healthcare system in conjunction with improving basic health insurance, medical care, medical aid, etc.

China has the capability to act urgently and quickly by partnering with international collaborators. China will, together with international collaborators, harness individual and collective resources under the stewardship by UN and WHO to overcome barriers that impede treatment and address this global challenge (Figure 2).

ROADMAP TOWARDS ENDING TB EPIDEMIC IN CHINA

Based on the ambitious targets of the End TB strategy and the baseline TB incidence rate in 2015 (65/100,000 population), the phased indicator of TB incidence rate in China in 2025, 2030, and 2035 was 33/100,000, 13/100,000, and 7/100,000, respectively. The End TB targets are deliberately ambitious, and any single intervention is unlikely to achieve these goals. Policymakers must identify what interventions and at what level of scale up will be needed to meet the End TB targets at the country level. The main interventions including optimizing the use of existing tools enabled by investments in universal health coverage to scale up

the active case-finding targets and improve TB preventive treatment among high-risk population to adopt and scale up novel tools (diagnostics, drugs, and vaccines) (Figure 3).

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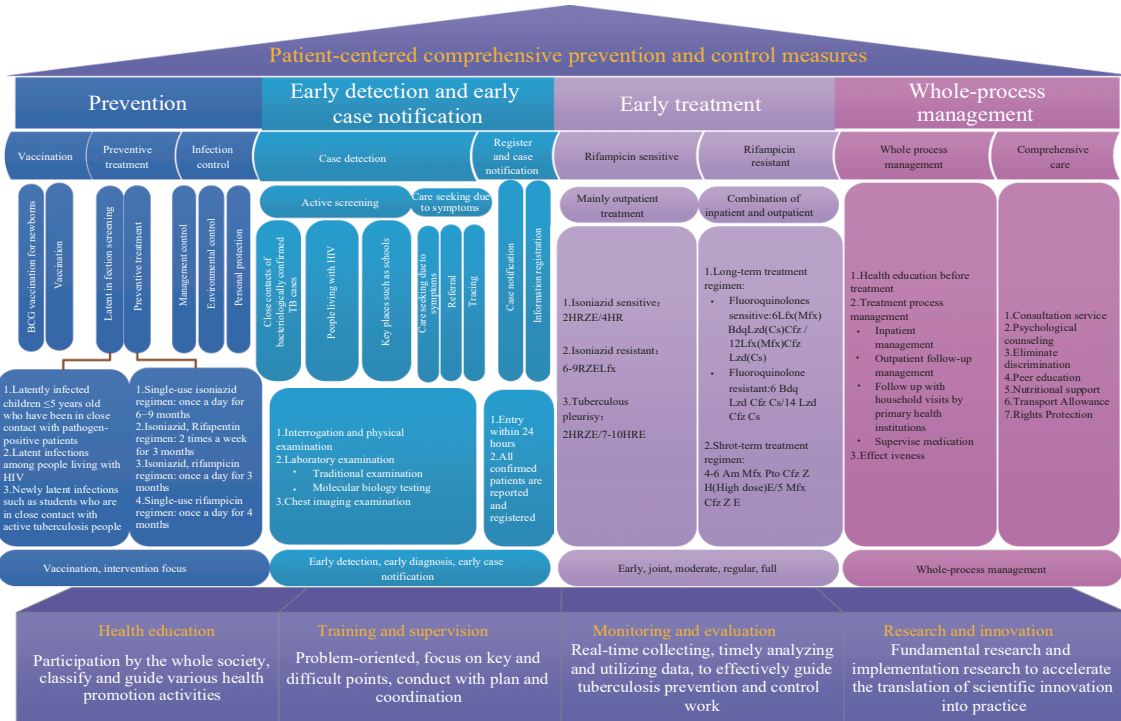


FIGURE 2. Tuberculosis control and prevention key measures.

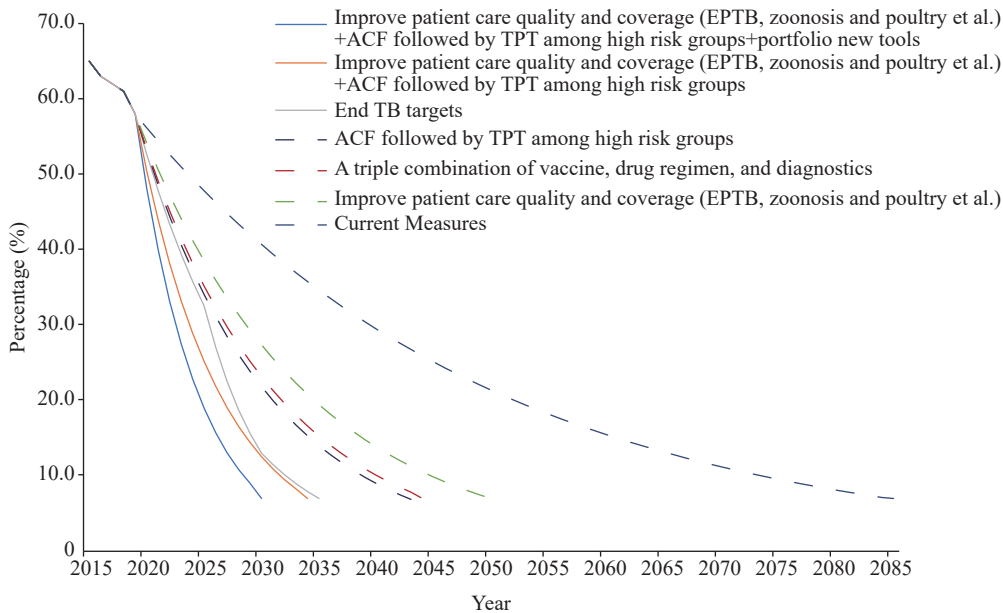


FIGURE 3. Roadmap towards ending tuberculosis epidemic in China.

Abbreviations: ACF=active case finding; TPT=latent TB=preventive treatment; EPTB=extra pulmonary tuberculosis

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Preplanned Studies

National Proficiency Testing of Molecular Diagnostics for Tuberculosis and Drug Resistance Detection — China, 2014–2019

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Summary

What is already known about this topic?

Proficiency testing (PT) is a key component of quality assurance and is essential in ensuring accurate laboratory diagnosis of tuberculosis (TB) and drug-resistant TB. The National Tuberculosis Reference Laboratory (NTRL) developed a novel PT panel to test laboratories' proficiency for molecular TB diagnostic assays throughout the TB laboratory network. A total of 6 PT rounds for molecular diagnostics were conducted by NTRL from 2014 to 2019.

What is added by this report?

PT conducted using artificial sputum specimens increased from 120 in the first round to 1,835 in the sixth round. Overall, laboratories demonstrated good proficiency for MTB and drug-resistance detection by molecular diagnostics, which is evident from the qualification rates over the six rounds: 95%, 97%, 96%, 93%, 93%, and 97%, respectively.

What are the implications for public health practice?

The use of artificial sputum specimens for PT panel production to test TB molecular diagnostics in China is feasible. Most of the participating laboratories provided reliable molecular diagnostic results for MTB and drug-resistance detection. The TB laboratory network can be instrumental in implementing PT expansion and improving the quality of TB molecular diagnosis in China.

China has made significant progress in establishing a well-coordinated tuberculosis (TB) laboratory network (1). The national TB laboratory network is composed of four levels of laboratories: national, provincial, prefectural, and county. The National TB Reference Laboratory (NTRL) is responsible for the development of the national plan for TB lab services and provides training and guidance to lower-level TB labs. NTRL

leads the provincial-level TB reference laboratory (PTRL) plan and oversees the services provided by prefectural and county-level TB labs to ensure quality and compliance with biosafety regulations.

Over the past few years, several new commercial molecular diagnostics have been recommended by the World Health Organization (WHO) (2–4). In addition, several locally manufactured molecular diagnostics were certified for use by China's National Medical Products Administration (NMPA) (5–7). Following this, in 2013, the Global Fund procured 925 GeneXpert and 125 GenoType MTBDRplus instruments for China along with test reagents. China's "13th Five-Year" National Tuberculosis Prevention and Control Plan (for implementation by 2020) mandated that all TB-designated hospitals at the prefecture level shall have the ability to carry out molecular diagnosis of TB, 80% of counties in the eastern and central regions and 70% of counties in the western regions shall have the capacity to carry out molecular diagnosis of tuberculosis. With past and future rapid scale up of TB molecular diagnostics across the country, there has been and remains an urgent need for a proficiency testing (PT) program to ensure the quality of these new testing platforms (8). PT for TB molecular diagnostics was first launched in 2014, and as of 2019, six rounds have been completed. This was the first study in China that systematically assessed the procedures and results of the nationwide proficiency testing of molecular diagnostic tools.

Each PT panel contained 10 artificial sputum specimens with the following characteristics: 2 rifampin (RIF) and isoniazid (INH)-susceptible mycobacterium TB complex (MTBC), 2 RIF and INH-resistant MTBC, 2 RIF-resistant MTBC, 1 INH-resistant MTBC, 1 non-TB mycobacterium (NTM), and 2 negative for TB. All PT panels were transported from the NTRL to targeted provincial TB reference laboratories (PTRL), and each of these

provincial sites were then arranged for distribution of panels to prefecture and county-level TB laboratories. All transport and storage of panels from the NTRL to the final testing sites was done with strict observance of cold chain.

All laboratories capable of molecular diagnosis of TB were required to participate in the PT plan. Once testing of PT panels was completed, all PTRL were responsible for collection and submission of test results (from participating laboratories) to NTRL. The NTRL compared the submitted test results with the reference results for each participating laboratory. Laboratory sites passed PT and determined as qualification if their results had no errors in the qualitative diagnosis of MTB, rifampicin, or isoniazid resistance or only had one sample with no test result (i.e. test failure). NTRL issued certificates acknowledging the type of molecular diagnostic platform used, provided results feedback, and discussed findings with the staff of all participating laboratories.

The number of participating laboratories from the first to sixth rounds of PT increased each year. Laboratory participation increased from 120 in the first round to 1,835 in the sixth round. Laboratories participating in the first round of PT were predominantly provincial and prefectural-level facilities and had a qualification rate of 95%. The second round of testing technology is GeneXpert with a qualification rate of 97%. With the increase in the number of county-level testing labs and the types of diagnostics, the qualification rates of the fourth and fifth rounds dropped to 93%. After national and provincial-level training programs were strengthened, the sixth-round qualification rate increased to 97% (Figure 1).

Except for the first round of testing, which did not include county-level TB labs, all other rounds of PT

were primarily performed at county-level TB labs, which accounted for 72% (966/1,341) and 75% (1,370/1,835) at the fifth and sixth round PT, and 4 third-party medical testing centers joined in the sixth round (Figure 2).

The type of participating facilities transitioned from CDCs and TB dispensaries in the first four rounds to TB-designated hospitals in the fifth and sixth rounds. TB-designated hospitals accounted for 65% (1,199/1,835) in the sixth round (Figure 2).

A total of 1,971 sets of PT panels were tested by a variety of molecular diagnostic platforms in the sixth round PT plan, and the qualification rate was 96.3% (1,899/1,971). Of all participating facilities, most were county-level facilities, accounting for 75% (1,370/1,835). The qualification rates at the provincial, prefectural, and county-levels were 97% (69/71), 94% (366/390), and 97% (1,331/1,370), respectively. The qualification rates of TB-designated hospitals and CDC/TB dispensary were 97% (1,155/1,196) and 96% (610/633), respectively.

All the provincial labs carried out Xpert MTB/RIF testing in the six round PT, three isothermal amplification diagnostics were covered in a total of 20 provincial-level administrative divisions (PLADs). Except Xizang (Tibet), all provincial labs have molecular drug sensitivity testing capabilities. Xpert MTB/RIF (48%, 953/1,971) was the most predominant molecular method, followed by Defast.TB (14%, 285/1,971), EasyNat (13%, 255/1,971), MeltPro TB (7%, 144/1,971), real-time PCR (5%, 100/1,971), GenoType MTBDRplus (5%, 98/1,971), Loopamp (4%, 74/1,971), and GeneChip MDR TB (3%, 62/1,971).

Different molecular diagnostic tools had different qualification rates in the sixth PT plan. EasyNat has

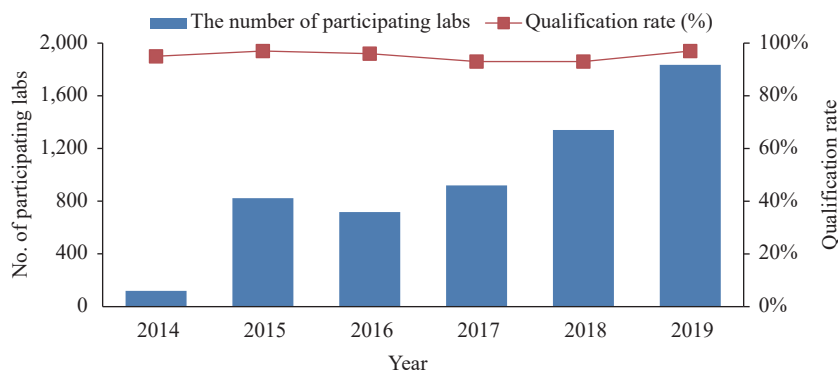


FIGURE 1. Number of participating labs and qualification rate for proficiency testing.

Note: The data on the left axis represents the number of participating labs. The percentage on the right axis represents the qualification rate of participating labs.

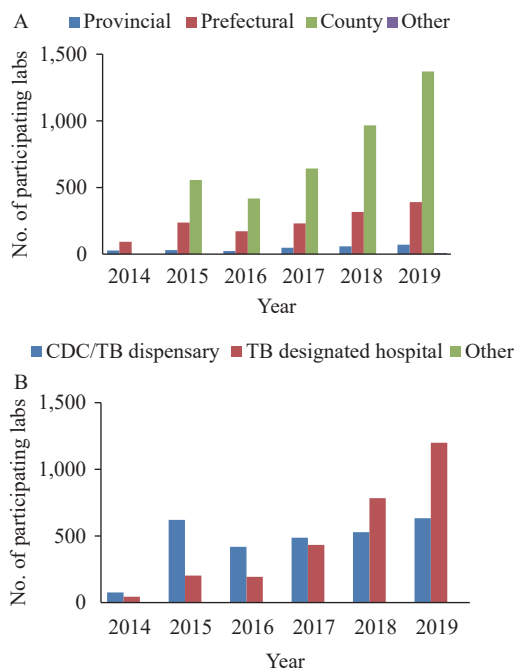


FIGURE 2. Levels and types of participating units in proficiency testing.

Note: The data on the left axis represents the number of participating labs.

the lowest qualification rates at 92% (234/255), with error types being mainly false negative for MTB detection and appeared more than once in some labs. Xpert MTB/RIF had the highest qualification rates at 98% (931/953).

The false positive rate of unqualified MTB detection was 16% (19/119), while the false negative rate of unqualified MTB detection was 63% (75/119). A small number of laboratories encountered problems with identification of non-tuberculous mycobacteria (NTM) and drug susceptibility testing to RFP and INH, 7 samples were misdiagnosed as MTB, and 10 samples of RFP and 7 samples of INH susceptibility test results were incorrect (Table 1).

DISCUSSION

Quality assurance is intended to ensure the quality of the overall testing process (8). The NTRL provides quality assurance through technical, biosafety, and managerial training; proficiency testing; and onsite supervisory. The aim of this study was to systematically analyze the performance of TB laboratories for detecting MTB and drug susceptibility through a limited series of PT rounds. This evaluation identified common problems at the laboratory level, assessed staff

TABLE 1. List of different error types for unqualified samples listed by different molecular techniques in the six rounds of proficiency testing plans.

Diagnostic tool	NTM		MTB		DST							
	Identification error	False positive	False negative	Failure	False RFP susceptible	False RFP resistance	RFP test failure	False INH susceptible	False INH resistance	INH test failure	INH susceptibility test failure	subtotal
Loopamp	1	3	0	0	NA	NA	NA	NA	NA	NA	NA	4
EasyNAT	0	2	50	0	NA	NA	NA	NA	NA	NA	NA	52
DeFast.TB	3	6	16	0	NA	NA	NA	NA	NA	NA	NA	25
Real time PCR	2	3	2	0	NA	NA	NA	NA	NA	NA	NA	7
Xpert MTB/RIF	0	5	4	25	6	1	1	NA	NA	NA	NA	42
GenoType	0	0	1	0	0	1	0	0	3	0	0	5
MTBDRplus	0	0	2	0	0	0	4	0	0	4	0	11
GeneChip MDR TB	1	0	0	0	0	0	0	1	3	0	0	7
MeltPro TB	0	0	0	0	0	2	1	1	3	0	0	7
Total	7	19	75	25	6	4	6	1	6	4	4	153

Note: The NA is the abbreviation of not available.

Abbreviations: MTB=mycobacterium tuberculosis; NTM=non-tuberculosis mycobacteria; PCR=polymerase chain reaction; DST=drug susceptibility test; RFP=rifampicin; INH=isoniazid.

and management training needs, and highlighted the potential benefits of a long-term, permanent PT plan for all TB diagnostic testing sites in China.

This study identified that participation rates in PT plans were relatively low at first, which was likely due to not all laboratories performing molecular diagnostics routinely and the NTRL just carrying out PT for Global Fund project sites that had already been equipped with GenoType MTBDR and GeneXpert equipment. The 13th Five-Year National Tuberculosis Prevention and Control Plan stipulated that each PLAD initiate molecular testing for TB detection and provide financial support for participation in PT plans, which all contributed to the successful implementation of the fifth and sixth rounds of PT plans. This is an example of the value of national policy working hand-in-hand with national public health programs to improve quality of diagnostic testing.

Overall, the participating laboratories demonstrated good performance during the PT plan. Contamination was the most serious concern for clinical laboratories' use of molecular diagnostics. To avoid contamination during panel sample preparation, all of the PT samples were prepared by anti-contamination operations in a biosafety-level III laboratory. The false positive rate for unqualified MTB detection was 16% (19/119) in the sixth round of PT. Five negative samples were read as positive by Xpert MTB/RIF, which is a reminder that even with fully automated integrated testing equipment, test personnel still need to strictly adhere to the standardized operating procedures and should regularly clean and maintain testing equipment to avoid contamination (9).

In this study, we also found that some positive PT samples produced negative results, which could have been due to the following reasons: failure of nucleic acid extraction, instrument failure, or problems with test reagents. Once again, this illustrates the need for laboratory staff to do the following: 1) strictly follow the standardized operating procedures for nucleic acid extraction; 2) strictly follow the kit manufacturer's instructions and requirements for reagent transportation and storage; 3) regularly check and calibrate the consistency of the temperature control of the thermal cycler; and 4) speed up the development and application of automated testing equipment for nucleic acid extraction, amplification, and detection.

Some other problems seen in individual laboratories included clerical errors, incorrect interpretation of test

results, and test failure issues. These problems may be indicative of more general problems in laboratory practice and should be corrected by implementing a laboratory quality management system. Corrective actions concerning interdependent quality management systems activities could include the following: conducting staff training and refresher training in case of operator-related non-conformities; maintaining and updating registers; monitoring quality indicators; reviewing sample referral systems; and improving and updating the infrastructure of laboratory facilities. In addition, laboratory practices may be subject to the Hawthorne Effect, in which site performance improved due to regular quality assessment, so that PT should be combined with technical training and onsite supervisory to perform better quality assurance.

This study was subject to two limitations. First, not all laboratories capable of molecular diagnosis of TB had participated in the PT plan. With more policies and strategies having been enforced, this situation has been changed greatly in the sixth round PT plan. Second, the cold chain requirement is likely to be a risk and cost issue in our PT plan, but the liquid specimen we used had resemblance to clinical samples and were relatively cost-effective to produce. We overcame this difficulty to some extent by tapping into the national TB laboratory network.

In conclusion, this study suggests that it is possible to develop a PT program (for TB molecular diagnostics) in a country as large and populous as China and that the use of artificial sputum specimens was feasible for this purpose. This implementation study demonstrated that the participating laboratories showed good performance in all six PT rounds and TB laboratory networks can be instrumental in implementing PT for expanding and improving TB molecular diagnosis in China.

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Preplanned Studies

Implementation Performance of Tuberculosis Control in China: 2011–2020

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Summary

What is already known about this topic?

World Health Organization (WHO) launched END TB Strategy but performance of tuberculosis (TB) control in China hasn't been systematically evaluated after 2010.

What is added by this report?

All five key indicators monitored in national TB program (NTP) have kept with high level or got impressively improved from 2011 to 2020. There were some differences in the performance of indicators among different regions.

What are the implications for public health practice?

NTP indicators should be readapted to new strategies and requirements in future plan.

The results from previous national surveys showed that China had made great progress in TB control from 1990 to 2010 and had achieved the United Nations (UN) Millennium Development Goals (MDGs) targets before the target date (halving prevalence and mortality rates by 2015 compared with 1990 levels) (1). A new TB service network integrating “prevention, treatment, management, and patient care” has been established after that. In 2015, the World Health Organization (WHO) launched the post-2015 era END TB Strategy, in which 2020, 2035, and 2050 incidence and mortality milestones have been settled to measure global and regional progress in comparison to 2015 levels (2). There is a requirement for the national TB program (NTP) to evaluate its stage progress. Key indicators were derived from notification data collected from the national Tuberculosis Information Management System (TBIMS) (3). All five key indicators have maintained high levels or were significantly improved in the past decade. There were still some differences in the performance of indicators among different regions. The 14th Five-Year Plan will be a new start and NTP indicators should be readapted to the new strategies and requirements. The

implications and definitions of the overall arrival rate should be changed. More efficient diagnostic tests should be scaled up to increase the bacteriologically-positive rate. Furthermore, the current two separated drug resistance screening indicators could be combined together.

Analytical notification data was extracted from TBIMS, and 5 key indicators were calculated based on cases between January 1, 2011 and December 31, 2020. Considering the socioeconomic circumstances varying among the 31 provincial-level administrations (PLADs), the PLADs were divided into 4 regions based on general social development indicators: JJH (Beijing, Tianjin, and Shanghai); East (Hebei, Liaoning, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan); Central (Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan); West (Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet (Xizang), Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang).

The 5 key indicators were as follows:

- 1) Overall arrival rate was defined as the proportion of cases that ultimately arrived at TB designated health facilities among all pulmonary tuberculosis (PTB) or presumptive PTB cases reported in the National Notifiable Disease Reporting System (NNDRS) by non-designated health facilities.
- 2) Bacteriologically-positive rate was defined as the proportion of bacteriologically-confirmed cases through sputum smear, culture, or molecular tests among all PTB patients notified in TBIMS, with TB pleurisy not included.
- 3) PTB treatment success rate referred to the proportion of patients with “cured” or “treatment completed” outcomes after finishing standard treatment course among all PTB patients notified in TBIMS.
- 4) Drug susceptibility test (DST) -multidrug resistant (MDR)-TB high-risk population referred to the proportion of cases tested for rifampicin resistance among all MDR-TB high-risk populations notified in TBIMS.
- 5) DST-new cases was defined as the proportion of cases tested for rifampicin resistance among all new bacteriologically confirmed cases

notified in TBIMS.

The overall arrival rate increased from 93.5% in 2011 to 97.3% in 2020 nationwide (Table 1). The bacteriologically-positive rate initially declined then rebounded in past decades to finally reach 55.3% in 2020 (Figure 1). The treatment success rate of more than 7 million PTB patients involved in NTP from 2011 to 2019 was continuously higher than 93% (Figure 2). DST-MDR-TB high-risk populations and DST-new cases both started from low levels to reach levels higher than 90% (Table 1).

The performance of indicators in different regions did not always show the same trend nationwide except for overall arrival rate. The bacteriologically-positive rate in the JJH region has changed from the lowest (39.4%) in 2011 to the highest (58.6%) in comparison to that of other regions while its treatment successful rates were almost always the lowest in the whole period. JJH showed good performance in DST indicators for both high-risk populations and new bacteriologically-confirmed cases from the beginning even they also varied during the middle sections of the study period. On the contrary, the starting level of

DST indicators in East, Central, and West regions was relatively low; however, they quickly increased to more than 90% after descending in the first few years. Generally, indicators in the Central and East regions were higher than those in the West region, except that West PLADs showed better performance than central PLADs in the indicator of “DST-new cases”.

DISCUSSION

TB control in China continues making great progress since 2011. Five key indicators have maintained high levels or improved significantly. Based on these performances, the target of decreasing the incidence rate of PTB that was marked in the “13th Five-Year Plan for National TB Control (2016–2020)” has already been successfully completed, and its annual average decline rate (3.2%) is significantly higher than the global average (1.7%) (4).

The proportion of reported PTB and presumptive PTB cases arriving at designated hospitals maintained a high level after 2011. The high performance of referral work is the premise of guaranteeing patients involved

TABLE 1. The change of overall arrival rate and DST proportions in China and sub-national regions, 2011–2020 (%)*.

Item	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Overall arrival rate, %										
Nationwide	93.5	94.7	95.1	89.5	90.2	90.9	90.7	93.4	96.0	97.7
JJH	92.6	92.9	92.6	87.4	91.7	86.3	93.3	94.4	95.2	97.0
East	92.2	93.8	94.9	91.1	91.6	91.3	90.3	91.9	94.7	97.6
Central	96.6	96.8	97.7	92.8	93.1	94.7	94.0	94.9	96.8	97.7
West	92.6	94.3	94.7	85.9	86.7	88.3	88.5	93.4	96.6	97.8
DST-MDR-TB high-risk populations, %										
Nationwide	-	-	-	35.7	73.2	54.8	57.2	72.6	88.4	97.4
JJH	-	-	-	91.2	88.9	70.8	69.1	84.3	91.8	97.0
East	-	-	-	49.1	75.7	62.0	67.2	81.4	90.7	97.4
Central	-	-	-	36.2	76.2	50.6	57.4	69.5	84.1	97.3
West	-	-	-	16.0	66.3	48.2	45.2	65.7	89.3	97.5
DST-new cases, %										
Nationwide	-	-	-	18.8	26.7	22.8	33.1	60.2	80.4	93.0
JJH	-	-	-	57.5	28.5	45.5	48.0	85.6	95.4	95.4
East	-	-	-	24.9	26.4	28.6	45.6	72.9	84.3	93.4
Central	-	-	-	14.4	22.8	17.7	23.4	50.1	74.2	91.2
West	-	-	-	16.2	32.9	21.1	31.0	55.6	81.5	94.1

Note: JJH: Beijing, Tianjin, and Shanghai; East: Hebei, Liaoning, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan; West: Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet (Xizang), Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang, Ningxia, and Xinjiang; -: not available.

Abbreviations: DST=drug susceptibility test; PTB=pulmonary tuberculosis; MDR-TB=multidrug resistant tuberculosis.

* Monitoring of DST proportion of MDR-TB started from 2014.

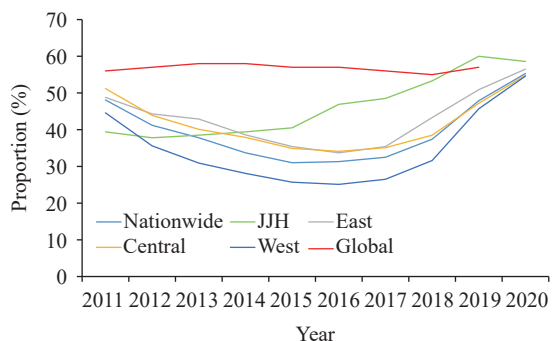


FIGURE 1. The change of bacteriologically-positive rate in China and sub-national regions comparing to global level, 2011–2020.

Note: JJJ: Beijing, Tianjin, and Shanghai; East: Hebei, Liaoning, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan; Central: Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan; West: Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet (Xizang), Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang.

in NTP diagnosis cascade and initiation of standardized treatment. Meanwhile, the adaption of this indicator also reflected essential implication for China's NTP patients management work. Before 2014, the overall arrival rate was only monitored among TB patients reported in resident county. With expansion to reported patients outside resident counties, NTP has greatly enhanced its migrant patients management since 2014. Therefore, it declined at the beginning of strategy changing but quickly rebounded and reached at 97.7% at the end of 2020.

The proportion of bacteriologically-confirmed cases among PTB patients has raised to 55.3% in China in 2020. It has already met the requirement (50%) posted in the National "Stop TB Action Plan (2019–2022)" (5) but was still relatively low comparing to other countries. In 2019, bacteriologically-confirmed cases accounted for 57% of PTB worldwide and about 80% in high-income countries (4). This indicator also fluctuated, which may be related with the changing of TB diagnosis and treatment service models. General hospitals historically preferred to use imaging methods to clinically diagnose TB rather than perform bacteriological examinations for every patient. Therefore, the bacteriologically-positive rate has declined more than one-third nationwide in the first several years. The decline was also affected by the scale of system reforming. In the West where most treatment centers were previous CDCs and shifted to general hospitals, the bacteriologically-positive rate declined by almost half. While in JJJ areas where the

service systems were relatively stable, the rate only declined slightly at the beginning and then increased step by step.

Another indicator with a stable high level is the treatment success rate that contributed to a relatively low TB death burden. The mortality rate in China fell by 35.3% from 2011 to 2019 and became the lowest in 30 High Burden Countries (4). But several challenges still exist. Ageing could be a serious problem in the future for China's TB control, especially in big cities and eastern PLADs (6). In our study, the relative lower treatment success rate in the East and JJJ (Beijing, Shanghai and Tianjing) also remain concerning.

The coverage of drug susceptibility tests increased significantly in recent years. The proportion of drug resistance test screening among high-risk populations has reached a high level, which can be attributed to the continuously strengthened drug-resistant TB control strategies, e.g. scaling up the coverage of new diagnostic tools, involving screening expenditure to social medical insurances. As a result, the number of identified laboratory-confirmed rifampicin resistant (RR)-TB or MDR-TB cases has increased from 5,807 in 2014 to 18,246 in 2019 (4). But on the other hand, we should also notice that it is not enough to only screen among high-risk populations. The RR rate of new patients in China is also high and has raised from 6.7% in 2007 (7) to 7.1% in 2013 (8), which is about 2 times the average level of MDR-TB high burden countries. These types of patients are especially concerning and need to be found among new patients.

Our study has limitations. These five key indicators can not describe the whole complete frame of China's NTP practice. There were still many challenges and barriers that need to be carefully analyzed and addressed in future studies. In addition, our study only focuses on the performance of patients involved in the national surveillance system. There were still considerable TB patients not notified in TBIMS (9) that need to be further investigated.

All five key indicators has been greatly improved in the past decade, but the road towards a "Zero TB" world remains difficult. The 14th five-year plan will be a new start and NTP indicators should be readapted to new strategies and requirements. More and more designated centers were referred to general hospitals, and institutional referral may not be the focus for patient detection. Instead, all the reported patients should be restrictly involved in NTP management and the implication and definition of the overall arrival rate

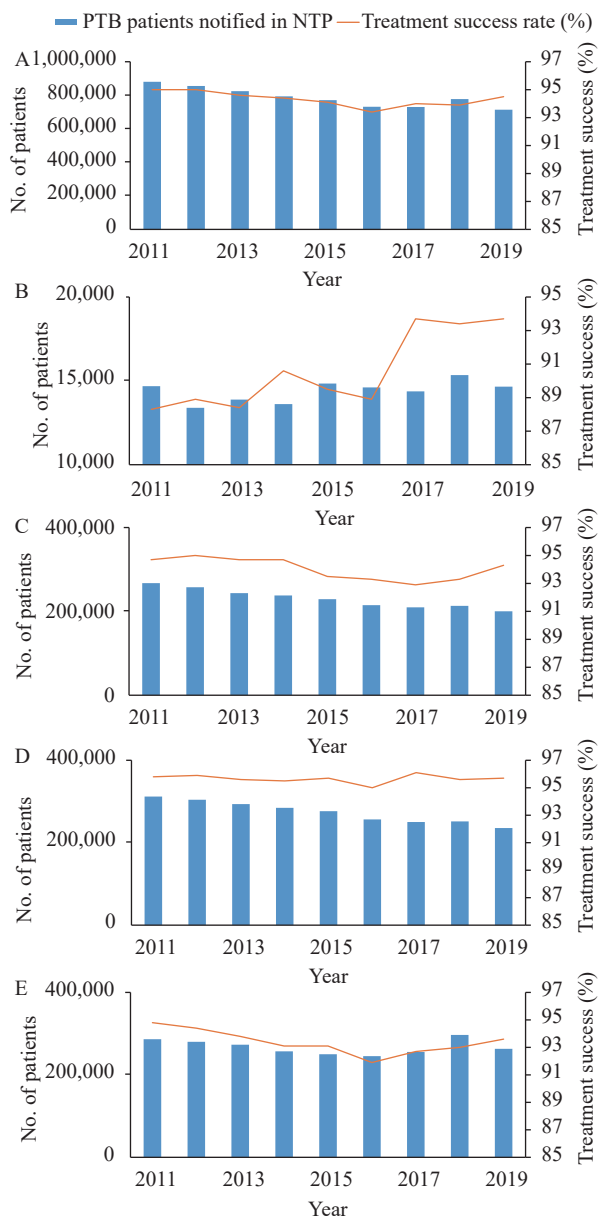


FIGURE 2. Number and treatment success rate of PTB patients notified in NTP in China and subnational areas, 2011–2019. (A) Nationwide; (B) JHJ (Beijing, Shanghai and Tianjin); (C) East; (D) Central; (E) West.

Note: Result of successful treatment rate for PTB patients notified in 2020 cannot be evaluated yet at the moment of assessment. JHJ: Beijing, Tianjin, and Shanghai; East: Hebei, Liaoning, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan; Central: Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, and Hunan; West: Inner Mongolia, Guangxi, Chongqing, Sichuan, Guizhou, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang. Abbreviations: PTB=pulmonary tuberculosis; NTP=national TB program.

should be changed accordingly. Monitoring and scaling up more efficient diagnostic tests (e.g. rapid molecular tests) to increase the bacteriologically-

positive rate will ensure patients are correctly diagnosed and receive effective treatment as early as possible, which can both benefit treatment outcomes and be the premise of drug resistance screening. Furthermore, the two separated drug resistance screening indicators can be combined into DST proportion among bacteriologically-positive patients.

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Commentary

Implementing New Approaches to Tuberculosis Control

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As someone who has studied tuberculosis (TB) for many years, it is difficult for me to admit, but tuberculosis has not been the most exciting field in medicine for a long time. The vaccine that is used in much of the world was developed in the 1930s. The foundational clinical research that defines how we treat TB was performed in India in the 1960s. And the last new drug to enter the TB armamentarium was introduced in many countries almost 30 years ago.

This slow pace has had an important consequence. Over the last few decades the emphasis in public health has moved from new therapies to doing a better job of implementing what we already have. This means that basic public health measures, including large-scale diagnostics, contact tracing, drug supply logistics and ensuring that patients are able to complete long treatment courses, have become the leading edge in efforts to control TB.

But changes are on the horizon, with both challenges and opportunities emerging in TB intervention. New diagnostics, new treatments and, potentially, new ways to prevent TB have the potential of dramatically changing how we approach disease, both at the level of the individual patient and also for the uninfected public. But employing these new tools is going to require reinvention at the level of implementation. And they must be applied in a landscape of significant and increasing drug resistant disease. Thus, the challenge of the next several years is not only going to be in developing tools but also determining how we're going to use them to produce real change.

THE PROBLEM OF DRUG RESISTANCE

Antibiotic resistance in TB is hardly a new problem. Very early after the introduction of streptomycin patients were seen to fail monotherapy. And, since the disease is transmissible, resistance could easily spread in the population. That problem could be mitigated, to some extent, using combination therapy. In theory, this could limit the evolution of new drug resistance as combinatorial selection makes escape mutations much

less likely.

However, practice has not kept up with theory. As each new antibiotic was developed, it was introduced into populations that had already serially acquired individual resistance mutations to the existing drugs. This was exacerbated by inappropriate prescribing, inconsistent drug supply and imperfect patient compliance all leading to increased development and subsequent transmission of drug resistant TB. To make matters worse, many countries and localities have little ability to detect drug resistance. In the most recent World Health Organization (WHO) report (1), of 10 million worldwide incident TB cases, 465,000 are thought to be multidrug resistant. This is a frightening number but is also undoubtedly an underestimate. Because drug resistance is either detected late or not at all, many patients are being treated inadequately, resulting in greater morbidity and mortality and unchecked transmission of resistant strains.

BETTER DIAGNOSTICS

For close to a century we've relied on two approaches to definitively diagnose TB. Sputum smears are fast but relatively insensitive while culture is highly sensitive but extremely slow. Fortunately, this has changed dramatically in recent years. The most dramatic results have come from culture-independent methodologies that result from the combination of engineering, genetics, and biochemistry such as the GeneXpert MTB (2) and TrueNat MTB (3) devices. These have two substantial advantages. They are very rapid and can provide answers directly from sputum. And these tests can not only diagnose disease but can simultaneously predict drug resistance. These tests come on the heels of other technical improvements, including the growing use of broth culture methods which can also accelerate growth.

Of course, these new technologies are only useful if they are actually used. New devices and the supplies they require are prohibitively expensive for most endemic parts of the world even after international subsidies. Reference labs that perform reliable culture-

based testing, which is essential for quality control in TB control programs, are not widely available. As multidrug- and extensively drug-resistant TB become more widespread, traditional drug susceptibility testing for second- and third-line drugs becomes even more important. Yet labs capable of reliably testing for these antibiotic susceptibilities, like the excellent lab at the Chinese CDC, are unavailable in most of the world. And, finally, how the information generated in the lab gets translated into practice remains problematic.

MORE EFFECTIVE THERAPIES AND TREATMENT STRATEGIES

The current therapeutic strategy for TB has served us fairly well for a long time. In controlled circumstances, cure rates are very high, 90%, at least for drug-susceptible disease. Unfortunately, real-world results still translate to an estimated >1.2 million annual deaths (1). There are many reasons for this. Patients are lost all along the “TB care cascade,” with many never diagnosed, others never getting connected to care following their diagnosis, others not having access to drugs, and still others starting but not completing therapy (4). There is no question that the cumbersome and extended multidrug course of therapy is a contributor to our frustratingly high failure rates. In addition, rising drug resistance rates mean that many patients receiving standard therapy are being inadequately treated with very high failure rates.

The problem with current therapy is two-fold. The length of therapy means that a substantial infrastructure needs to be built to ensure compliance — though infrastructure is expensive and, as shown by failure rates, doesn’t always work. And our treatments for drug resistant disease are typically even longer, with higher failure rates.

Over the past few years we have seen real changes, however. Several new antibiotics have entered the TB armamentarium. For most of these, there is no real pre-existing resistance, so they are active against circulating drug resistant *Mycobacterium tuberculosis* (Mtb) strains. Three novel classes of antituberculous drugs are now available and more are on the horizon. Bedaquiline (5), an inhibitor of the mycobacterial ATP synthase, is a very potent drug. Relative resistance is rare, though there is cross-resistance with the third-line agent clofazimine so that there is some pre-existing resistance (6). Two nitroimidazoles, delamanid (7) and pretomanid (8), have nearly identical mechanisms but pre-existing resistance is rare if it exists at all. And

linezolid, an oxazolidinone drug, is not new but has been shown to be useful for drug-resistant disease (9). Because it is not widely used, pre-existing linezolid resistance is uncommon. Using these drugs in combination with existing second- and third-line agents has resulted in much higher cure rates for drug-resistant TB. And, most intriguingly, an open label clinical trial showed that using only three oral drugs, bedaquiline, pretomanid and linezolid, resulted in high cure rates within six months in patients with either extensively- (XDR) or multidrug-resistant (MDR) TB who had failed or could not tolerate other regimens (10). These regimens hold great promise for many patients, many of whom were previously untreatable.

For several years, preclinical animal studies have suggested that there might be treatments that could result in a shorter course of treatment for drug-susceptible disease. Until this year, however, clinical trials have been disappointing. But a recently announced trial (unpublished as of the date of writing) has shown that a standard regimen that includes rifapentine instead of the rifampin together with added moxifloxacin for four months with directly observed therapy is non-inferior to the standard six month regimen. And animal experiments that test combinations including new drugs could make that even shorter (11). Given the potency of the recently released agents, it might even be possible to arrive at a “universal regimen” that could simultaneously be shorter and be used to treat all patients regardless of drug resistance. Given the toxicity of some of the newer drugs, particularly linezolid, more work will have to be done before we get there, but it remains an aspirational goal.

THE POSSIBILITY OF PREVENTION

Most of the world, including China, administers the *Mycobacterium bovis* BCG (BCG) vaccine. This agent, developed in the 1930s, helps to prevent the devastating consequences of childhood TB but has little efficacy in controlling TB in adults. There has been a long search for a better vaccine that could offer protection to adults but, until recently, trials have been disappointing. However, over the past two years, two studies have shown at least some promise. One suggested that revaccination of adolescents with BCG might protect against persistent Mtb infection (12). Another used a new adjuvant together with a fusion of two Mtb protein antigens, had efficacy of 50% in preventing progression of infection to disease over the

course of three years (13).

These new strategies are still far from clinical application. But they do suggest that it is possible to achieve better protection in adults than is afforded by BCG. Having even a partially-effective vaccine could change the TB control landscape, though how much of a change it would bring about would entirely depend on its performance characteristics.

THE CHALLENGE OF IMPLEMENTATION

The early experience with rolling out vaccination against COVID-19 has brought one aspect of disease control into sharp relief — the vaccine is only as good as the implementation strategy that utilizes it. This lesson has long been clear in TB control. Right now, we have good diagnostics and effective and inexpensive drugs, even if they can be improved. But they are being implemented inconsistently around the world, resulting in a huge number of preventable deaths. Having a strong TB control program is the best weapon we have both to ensure proper treatment of individuals and also, because treatment is our best form of prevention, protecting public health.

But rapid change is a challenge to even the best TB control programs. After all, one of the reasons that these programs can be successful is that they are standardized, ensuring the same care to all patients. However, some of the new technologies require much more individualization, particularly when it comes to drug-resistant disease. And changing even standardized approaches can be very difficult in large and bureaucratic organizations. In fact, many of us have heard from programs that would prefer to stick with older paradigms even when new interventions are demonstrably superior.

Because there are so many new aspects of diagnosis and treatment, it is now time to embrace change and make it an integral part of TB control. Measures that might help include:

- Algorithms that account for the varying speed and sensitivity of newer diagnostics. It would be simpler if any given country adopted a new diagnostic modality at all nationwide sites simultaneously. This will not happen. Instead, TB controllers are going to be faced with different types of information on each patient at each site. They will need help in understanding how to interpret these tests and what each finding should

trigger for treatment and contact tracing.

- Rapid recognition of drug resistance. Earlier appropriate treatment is associated with decreased transmission but, in many programs, resistance isn't recognized until clinical failure occurs. Finding patients with drug resistance not only benefits them but has important consequences for public health.
- An ability to rapidly incorporate advances in therapeutics. WHO guidelines are changing rapidly and the pace of change is likely to accelerate. Not all drugs are equally accessible in all parts of the world. But some of these hold the promise of having a significant impact on individuals and populations. TB control programs should be planning for how they will change rather than simply responding to new guidelines when they arise.
- Creating structures for individualized therapy. Identifying and optimally treating drug resistant TB requires a separate pathway within control programs. The best programs not only diagnose drug resistance early but also create individualized treatment regimens based on the specific resistance profiles of isolates. This can be accomplished either through expert guidance for each individual or, perhaps more practically, through predefined algorithms that change as new information becomes available. In fact, most clinical trials have been performed with patients with varying degrees of drug resistance, enabling the creation of appropriate algorithms.
- Integration or, at least, coordination with HIV treatment programs. Patients, particularly those with low CD4 counts, benefit from starting HIV treatment early when TB is diagnosed. And a single program is best suited to monitor drug-drug interactions between antiretrovirals and TB antibiotics.

We live in an exciting time for TB control. After decades of incremental changes we are on the edge of substantive advancements in how we approach the identification, treatment and prevention of TB. But they will only make a difference if we can apply them across the spectrum of translation, all the way from the lab to the public health program.

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Commentary

The COVID-19 Pandemic and Elimination of Tuberculosis in China

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One of the best kept secrets in global public health is how China achieved the tuberculosis (TB) targets in the United Nation's Millennium Development Goals (MDG). The MDG's TB targets were to reduce the prevalence and mortality of TB by 50% between 1990 and 2015. By 2010, China had reduced its TB prevalence and mortality by 65% and 80%, (1–2) which meant China exceeded the MDG targets 5 years before the MDG deadline. This impressive achievement helped China to move from a high to a medium TB-incidence country. Today, China still has the world's third highest number of new TB cases each year. But when adjusted for population size, it has the lowest TB incidence per capita among the 30 high TB-burden countries (3).

In 2015, the global community committed to the 2030 Sustainable Development Goals (SDG), which included two new TB targets — reducing TB incidence and deaths by 80% and 90%, respectively, compared to their 2015 levels (3). World Health Organization (WHO) went further by setting the 2035 END TB targets of reducing TB incidence and deaths by 90% and 95%, respectively (3). WHO estimates that China's TB incidence in 2015 was around 65 cases per 100,000 population (4). A 90% reduction would bring TB incidence to less than 7 cases per 100,000 population, a level seen in most high-income countries. Achieving this will mean that China has eliminated TB as a major public health problem.

Although the SDG and END TB targets seem difficult to achieve, we can learn from how China achieved the MDG TB targets, which was made possible by China's renewed commitment to control major infectious diseases following the 2003 SARS epidemic (5). Today, we are in similar situation. China is once again impacted by the spread of another coronavirus. The country has been strengthening its health system to be more responsive to both current and future pandemics. Perhaps TB can once again benefit from the renewed focus on controlling infectious diseases. This commentary will discuss how China can apply the lessons and approaches from its COVID-19 response to make progress toward eliminating TB as a major public health problem.

LEARNING FROM SUCCESSES IN TB CONTROL FOLLOWING THE SARS EPIDEMIC

To achieve the MDG targets, China had to achieve an earlier set of global TB control targets: WHO's 2005 targets of finding 70% estimated TB cases and successfully treating 85% of them (5). Between 2000 and 2005, China implemented WHO's DOTS strategy nationwide through its CDC system (Table 1). The proportion of TB patients treated in the CDC system increased four-fold, and a much greater proportion of TB patients in China completed their treatment (1). This achievement was extremely important because, without this, China would not have achieved the MDG TB targets. In retrospect, among the 22 high TB-burden countries in 2005, China was the only country to achieve these WHO targets.

Three main factors contributed to the successes of TB control following the SARS epidemic (5). First and foremost, there was strong government commitment to improve the control of infectious diseases and reach the 2005 WHO TB targets. Governments at all levels were held accountable for 3 key TB targets: DOTS coverage, case-detection, and treatment success. Second, the government improved the public health system, including the development of an internet-based reporting system for notifiable infectious diseases. This greatly facilitated the reporting and follow-up of TB patients in the hospital system. Third, increased domestic and international resources were combined into a single plan focused on achieving the government targets.

NEED TO IMPLEMENT A NEW TB CONTROL MODEL

Despite the progress in controlling TB during the first decade after 2000, important challenges to the control of TB emerged during the second decade. First, drug-resistance surveillance studies in China documented a serious epidemic of multidrug-resistant

TABLE 1. Evolution of tuberculosis (TB) control models and approaches to eliminate TB following the COVID-19 pandemic.

	DOTS strategy as basis for old TB control model (2001–2010)	Transition to new national TB control model (2011–2020)	Post-pandemic acceleration toward TB elimination (2021–2035)
TB control network	<p>County/district CDC and township/village clinics form TB control network:</p> <ul style="list-style-type: none"> ● CDC: Responsible for diagnosis and treatment, reporting, and monitoring of township and village doctors in carrying out their TB control functions; traced TB suspects who did not come for evaluation after being referred; responsible for maintaining program quality and achieving program targets. ● Township and village clinics: Doctors referred TB suspects to CDC for evaluation, traced those who did not reach CDC, and monitored patient's treatment in community. ● Hospitals: Required to report and refer TB suspects to CDC. 	<p>Designated hospitals for TB, county/district CDC, and township/village clinics form 3-in-1 TB control network:</p> <ul style="list-style-type: none"> ● Hospitals: Designated county/district hospitals provide diagnosis, treatment and reporting of routine TB patients; city/prefectural hospitals responsible for MDR/XDR-TB diagnosis and treatment. Other hospitals required to report and refer TB suspects to designated hospitals ● CDC: Responsible for monitoring of township and village doctors in carrying out their TB control functions; traced TB suspects who did not come for evaluation after being referred; monitor reporting by hospitals. ● Township and village clinics: Doctors refer TB suspects to hospitals for evaluation, trace those who did not reach hospitals, and monitor patient's treatment in community. 	<p>Strengthening of health system to address COVID-19 pandemic can help TB:</p> <ul style="list-style-type: none"> ● Hospitals: Designated hospitals providing COVID-19 diagnosis and treatment will have the capabilities to treat complicated respiratory illnesses with improved infection control system; staff are more knowledgeable about respiratory infection control. Such capacities are now more decentralized down to county level and can improve TB treatment. ● CDC: Capabilities to identify, trace, screen, and quarantine contacts are widely available. These can be used for TB contract investigation. ● Township and village clinics: Doctors are much more aware of respiratory symptoms and diseases and are on the look out for patients with respiratory symptoms. They can help look for TB patients.
Technical approaches	<p>Implemented in CDC clinics as DOTS strategy:</p> <ul style="list-style-type: none"> ● Diagnosis: sputum smear microscopy and chest x-ray ● Treatment: Standard short-course chemotherapy with first-line TB drugs ● Management of treatment: Primarily provided by family members; some directly observed therapy, especially during intensive phase of treatment. ● TB surveillance system: internet-based disease reporting system allowed real-time reporting of TB suspects, and case-based electronic registry of notified TB cases. 	<p>Implemented in hospitals according to national TB diagnosis and treatment guidelines:</p> <ul style="list-style-type: none"> ● Diagnosis: CT scan and chest x-ray; smear microscopy, culture, and rapid molecular tests to detect <i>M. tuberculosis</i> and drug resistance. ● Treatment: Standard short-course chemotherapy with first-line TB drugs for drug-sensitive TB; second-line TB drug regimen for rifampin-resistant/MDR TB. Bedaquiline introduced as a new TB drugs. ● Management of treatment: Primarily self-administered or monitoring by family members; use of digital adherence technologies. ● TB surveillance system: internet-based disease reporting system allowed real-time reporting of TB suspects, and case-based electronic registry of notified TB cases. Capture TB data directly from hospital medical information system. ● Use of the digital medium: Provide online training for health care workers, track TB patients using the medication monitor. 	<p>Technical and programmatic approaches used in COVID-19 pandemic can apply to TB:</p> <ul style="list-style-type: none"> ● Diagnosis: Large-scale network of molecular testing down to county level; laboratory network of genomic sequencing available. This can be used for rapid molecular testing for TB on a large scale, including for drug resistance. ● Treatment: Specific COVID-19 treatment guidelines provided to hospitals and implemented rapidly. TB treatment, including for MDR/XDR-TB, can be implement the same way. ● Contact investigation: Health care workers are trained to elicit contact information and better understand the environments facilitating airborne transmission; patients are much more aware of who they have been in contact with. Use of electronic surveillance have improved contact identification. TB can use this for contact tracing, testing, and treatment for LTBI. ● Large-scale screening and testing of COVID-19 in communities: Health departments and health care workers have experience from community screening programs; this can be used to implement active case-finding for TB. ● Large-scale COVID-19 vaccination in communities: Health departments and health care workers gain experience from vaccination programs; this can be used to implement TB vaccination programs for adults. ● Information system: Data on COVID-19 cases quickly shared in real-time from health facilities to government and used to monitor pandemic. TB data from hospitals and other sources can be made available in real-time for monitoring.

TABLE 1. (Continued)

	DOTS strategy as basis for old TB control model (2001–2010)	Transition to new national TB control model (2011–2020)	Post-pandemic acceleration toward TB elimination (2021–2035)
Funding	<p>Predominantly domestic funding but with significant international contribution; funding, mostly provided from national level:</p> <ul style="list-style-type: none"> • Increasing amount of dedicated TB funding by central government; provincial and prefectural/county TB funding also increased. • Simple diagnosis and first-line TB drugs provided largely free of charge. Limited funds for township/village doctors to carry out TB services. • Funding from international organizations (World Bank, DFID, GFATM, JICA, CIDA, WHO) supported scale-up of DOTS strategy. 	<p>Entirely domestic funding, mostly provided by provincial and local governments:</p> <ul style="list-style-type: none"> • Dedicated TB funding by central government for first-line drugs and basic TB diagnosis; variable level of dedicated TB funding from provincial and local governments. • National health insurance important in paying for TB services provided by hospitals (including diagnosis, treatment, and hospitalization), but patient out-of-pocket (OOP) payment still substantial, especially for MDR-TB. • Government funding for township/village clinics to carry out public health functions, including TB services. • Supplemental funding provided by some government sources to reduce patient OOP expenses for TB services. 	<p>Government funding to strengthen pandemic preparedness and responsiveness can enhance support for TB:</p> <ul style="list-style-type: none"> • Funding to hospitals, CDC's, laboratory network, primary health care clinics, and health promotion can all potentially benefit TB diagnosis and treatment. • In addition to government insurance, government provided subsidies to reduce out-of-pocket payment for COVID-19 treatment. COVID-19 vaccinations free of charge. These can apply to provide entirely free diagnosis and treatment or substantially reduced cost of care for TB patients.

TB (MDR-TB) that was not being addressed (6). The CDC's were unable to diagnose or treat MDR-TB, and hospital treatment of TB was actually a risk factor for acquiring MDR-TB (6). Second, to focus the CDC system on its public health functions, the government began shifting TB diagnosis and treatment from the CDC's to the hospitals. This large-scale change carried certain risks because hospitals were not set up to provide community support to patients after they returned home to continue treatment, which often needed several weeks to months. A modeling study showed that a reduction in treatment quality from this shift could worsen the TB epidemic in China (7).

To address these challenges, a new TB control model was piloted by the China CDC under the guidance of the National Health Commission in collaboration with the Bill and Melinda Gates Foundation and then successfully implemented in 3 provinces (Table 1). The program had 3 important components. First, it fully incorporated the hospital system into the TB control network by designating county/district hospitals to diagnose and treat drug-sensitive TB and city-level specialized hospitals to diagnose and treat MDR-TB. Second, it incorporated innovative approaches to modernize TB diagnosis and treatment. Third, it increased the coverage of national health insurance for TB diagnosis and treatment, which reduced catastrophic health expenses for TB patients, especially those with MDR-TB.

These 3 components worked synergistically to improve diagnosis and treatment for TB, especially for MDR-TB (8). Take as an example a patient diagnosed

with TB in the designated county hospital. His sputum specimens were transported to the designated city hospital, where rapid molecular testing revealed that he had rifampin-resistant TB. The information was quickly sent to staffs at the county hospital, and they quickly tracked down the patient and referred him to the city hospital for treatment. After being hospitalized and started on appropriate second-line TB drugs, he was referred back to the county CDC, which arranged for regular follow-up by the township clinic. Although he was very poor, the rural health insurance scheme paid for a high percentage of his treatment cost, and he received additional subsidies from the Ministry of Civil Affairs' subsidies for very poor rural residents. As a result, he was able to complete his two-year treatment course. This example illustrates the importance of having all three components of the model functioning together.

HOW COVID-19 PANDEMIC CAN HELP ELIMINATE TB AS A PUBLIC HEALTH PROBLEM

China is still far from the SDG and END TB targets. Since 2015, the decline in TB incidence has been approximately 2% per year (4). Improved treatment of drug-sensitive TB over the past two decades have substantially reduced new TB infections. But approximately 20% of China's population, or nearly 300 million people, is already infected with *M. tuberculosis* (9), and TB from reactivation of latent TB

infection (LTBI) will continue to develop in huge numbers each year. In fact, a modeling study suggested that the vast majority of China's TB cases are now arising from LTBI (10). Without new interventions to address LTBI, it will take several decades for China to eliminate TB. At the same time, MDR-TB will remain a serious problem. The proportion of new TB cases with rifampin-resistance or MDR have not declined appreciably since the first National TB Prevalence Survey in 2007 (3).

The COVID-19 pandemic provides a new opportunity to take rapid steps toward the SDG and END targets and eliminate TB and MDR-TB as a public health problem. The government has strengthened the health system to respond to the pandemic. It has also implemented new technical and programmatic approaches to keep the pandemic under control. In addition, there is major government funding to support pandemic preparedness and responsiveness. All of these can be leveraged for TB (Table 1). Specifically, they can support three key programmatic interventions needed to eliminate TB as a public health problem.

The first intervention is to fully transition all provinces to the new TB control model described above (Table 1). For instance, many cities and counties still do not have the diagnostic network for rapid molecular testing of *M. tuberculosis* and drug resistance, the quality of MDR-TB treatment is not uniform, follow-up of these patients during outpatient treatment is suboptimal, and designated hospitals are not properly staffed for TB or have poor infection control standard. Many of the pandemic-related improvements can help China implement the new TB control model and build a robust system of TB diagnosis and treatment for years to come.

The second intervention is to scale-up use of TB preventive treatment (TPT). If China is to substantially accelerate the decline in its TB incidence, it must address the large reservoir of LTBI in its population. The most cost-effective approach is to target the population most at risk for progressing from LTBI to active TB — close contacts of active TB cases (11). Finding and evaluating close contacts frequently lead to additional TB cases. But the full benefit of contact investigation comes from providing TPT to the contacts with TB infection (12).

Up to now, TB contact investigation and provision of TPT to close contacts have not been effectively implemented in high TB burden countries. Part of this is due to the implementation challenges. Current losses

along the cascade to screen and treat individuals for LTBI is huge (13), raising the question of whether the benefits are worth the cost. But China has gained considerable experience with tracing and testing of COVID-19 contacts. This could be applied to TB. Shorter drug regimens — down to one month or 12 weekly doses — will make TPT much more feasible to implement (12,14).

The third intervention is mass administration of new TB vaccines when they become available. There are two promising vaccination approaches. First, a study showed that BCG revaccination of adolescents reduced the risk of *M. tuberculosis* infection by 45% (15). A larger clinical trial is now underway to confirm this observation in South Africa with results anticipated by 2024 or 2025. Second, a study of GSK's M72 vaccine demonstrated a 50% protection against progression to pulmonary TB in adults with LTBI (16). Planning for a phase 3 efficacy study is underway and the trial will likely begin early 2023 with results anticipated around 2028.

If one or both vaccine trials show efficacy in protection against TB infection or disease, vaccines will become important tools in the fight against TB. For China, with its high burden of LTBI, the availability of a vaccine that can prevent disease among latently infected persons will be especially important. Experience with rolling out COVID-19 vaccines in all age groups will help prepare for the rollout of new TB vaccines.

ELIMINATION OF TB AS A CRITICAL PART OF THE HEALTH SECURITY AGENDA

With the COVID-19 pandemic, the control of infectious diseases is once again high on the health and development agenda of the Chinese government. The government clearly recognizes the need to build the system and capabilities to respond rapidly and effectively to new epidemics. But the track record of governments around the world to prepare for new pandemics is poor. Following the 2009 H1N1 pandemic, an independent assessment found that the world was ill-prepared to respond to a global public health emergency (17). An assessment done prior to the COVID-19 pandemic found that most countries did not have sufficient capacity to detect and respond to a major epidemic (18).

Because many years could lapse between major pandemics, it is difficult to build and maintain a

responsive and prepared system to deal with a pandemic when it does occur. The main capabilities needed to be built and maintained are those needed to rapidly detect and treat an airborne pathogen and prevent its spread. These system and capabilities are precisely the ones needed to eliminate TB. Therefore, it makes sense to advocate for TB to be high on the health security agenda. The interventions needed to eliminate TB could be presented as the best way to build and maintain the health system's preparedness and responsiveness to a new pandemic.

Health security for China can work in synergy with the elimination of TB in the country. By implementing the recommended TB elimination interventions in this commentary as part of the government's health security agenda, China will be much closer to the SDG TB targets by 2030, and this could set the stage for China to be the first high TB burden country to eliminate TB as a public health problem by 2035 or soon thereafter.

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