Observational Study

Medicine®

OPEN

Epidemiological characteristics of pulmonary tuberculosis in Shandong, China, 2005–2017

A retrospective study

Ning-Ning Tao, MM[a], Yi-Fan Li, MB[a], Shan-Shan Wang, MD[a], Yun-Xia Liu, MD[b], Jin-Yue Liu, MB[c], Wan-Mei Song, MB[a], Yao Liu, MD[a], Hong Geng, MD[d,*], Huai-Chen Li, MD[a,*]

Abstract

This study aimed to analyze the epidemiology of pulmonary tuberculosis (PTB) and gained insight into the future TB control plan in China.

We extracted epidemiological, clinical, and geographic data from TB prevention and control institutions in 6 cities of Shandong province, China, during 2005 to 2017.

Among 224,480 diagnosed PTB, rural residents accounted for 93%, smear-positive PTB 52%, and new cases 92%. The incidence rate of overall PTB declined from 40.8 to 26.25 per 100,000 during 2005 to 2017. Except smear-negative PTB (7.57–19.87 per 100,000), the incidence of smear-positive PTB and all that stratified by age, sex, and treatment history decreased. With 80% reduction, the incidence of smear-positive PTB (6.38 per 100,000) and relapse cases (1.01 per 100,000) were already very low in 2017.

With persistent efforts to combat TB, the disease burden had shifted from smear-positive PTB to smear-negative PTB. While new cases need continuous attention, further reducing the incidence of smear-negative PTB and elderly patients may have a greater impact on future TB control.

Abbreviations: APC = annual percent change, CDC = Center for Disease Control and Prevention, CI = confidence interval, DOTS = directly observed treatment, short-course, DR TB = drug-resistant tuberculosis, DST = drug susceptibility testing, OR = odds ratio, PTB = pulmonary tuberculosis, SARS = severe acute respiratory syndrome, TB = tuberculosis.

Keywords: distribution, epidemiology, incidence, pulmonary tuberculosis

1. Introduction

Monitoring time trends and measuring the burden of tuberculosis (TB) is critical for the evaluation of whether global targets are achieved and for planning TB control interventions. To eradicate TB, the World Health Organization establishes the end TB strategy which outlines an overall goal of 90% reduction in incidence and 95% reduction in mortality, compared with 2015 baseline.[1] Although great achievements have been obtained for TB control, TB still develops into the leading cause of death from a single infectious agent, ranking above human immunodeficiency virus infection (HIV) and acquired immune deficiency syndrome.[1] Globally, 10 million people (64% new cases) suffer from TB and 1.6 million people die of TB in 2017.[1] It is uncertain if maintaining the current strategies will be enough for human to reach the 2035 target.[2]

Since 1990s, China has implemented a high-quality directly observed treatment, short-course (DOTS) strategy in Center for Disease Control (CDC) public health clinics in 13 provinces (including Shandong province) covering half the country's population.[3] However, only 30% of the estimated new smear-positive TB cases were treated under this program till 2000.[4] To accelerate the national TB control efforts, several strategies have developed since 2000. The Chinese government expanded the DOTS strategy nationwide with its free treatment policy to also cover active pulmonary tuberculosis (PTB) in 2000 and smear-negative PTB in 2005 (before 2000, free treatment were provided only for smear-positive patients).[5] Moreover, after the severe acute respiratory syndrome (SARS) epidemic was brought under control, the Chinese government increased public-health funding, revised laws on TB control, introduced internet-based disease reporting system, and rebuilt local public-health facilities to accelerate the performance of TB control programs.[6–8] With those strategies, a 48% reduction in bacteriologically positive TB and a 65% reduction in smear-positive TB were achieved between 1990 and 2010, dramatically contributing to the realization of the stop TB strategy.[4,5,9,10] However, China still ranks second among the 30 high TB-burden

Editor: Oliver Schildgen.

N-NT and Y-FL contributed equally to this article and shared first authorship.

This work was supported by the Science and Technology Development Plan of Shandong Province (grant number 2017GSF218052).

The authors have no conflicts of interest to disclose.

[a] Department of Pulmonary and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong University, [b] Department of Biostatistics, School of Public Health, Shandong University, [c] School of Medicine and Life Sciences, University of Jinan-Shandong Academy of Medical Sciences, [d] Centers for Tuberculosis Control in Shandong Province, Jinan, China.

[*] Correspondence: Hong Geng, and Huai-Chen Li, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China (e-mails: genghong123@sina.com and lihuaichen@163.com).

Medicine (2019) 98:21(e15778)

Received: 2 November 2018 / Received in final form: 6 April 2019 / Accepted: 30 April 2019

http://dx.doi.org/10.1097/MD.0000000000015778

countries and has the world's largest number of patients with multidrug-resistant.[1] TB remains an ongoing intractable health challenge in China.

Shandong, a province located on the east coast of China is the second largest province with a population of 95 million according to the Sixth National Census. In 2010, 211,900 people in Shandong were infected with TB.[11] The purpose of this study was to summarize the epidemiology of PTB from 2005 (the time internet-based TB reporting system was established) to 2017 among 6 cities of Shandong Province, China, to help plan effective intervention strategies for the prevention and control of TB in similar populations.

2. Material and methods

2.1. Ethical clearance

This study was approved by the Ethics Committee of Shandong Provincial Hospital, which is affiliated to Shandong University. Patient records were anonymized and de-identified before analysis.

2.2. Study population and data collection

This study covered 48.21% (6/17 cities, Jinan, Linyi, Weifang, Yantai, Dezhou, and Jining) population of Shandong province. All the monitoring sites in the 6 cities were included. Cities selection were based on convenience and reflection of a range of TB burdens and clinical capacities. PTB cases that occurred in the 6 cities during 2005 to 2017 were consecutively collected from the Shandong Information System for Disease Control and Prevention. Population data were collected from the Shandong Statistical Yearbook, covering the years 2005 to 2017 (http://www.stats-sd.gov.cn/).

In 2004, the Center for TB Control and Prevention of Shandong Province where trained researchers collected and recorded patient information on a standard form set up the Katharine Hsu International Research Center of Human Infectious Diseases. Since then the Katharin Hsu Center has been responsible for laboratory quality assurance and TB surveillance in Shandong Province.

We analyzed data with demographic information (sex, age, race, and stratum), geographic information and clinical information (result of smear microscopy, TB contact history, and prior TB treatment history).

2.3. Laboratory methods

All patients with presumptive PTB (cough for >2 weeks, fever for >2 weeks, weight loss, TB contact history or abnormal chest radiograph) were requested to submit 3 sputum specimens (spot, night, morning) for acid-fast bacilli (AFB) with Ziehl-Neelsen smear microscopy before the initiation of treatment. For purposes of internal quality control, all positive smears should be reconfirmed by another microscopist in the same laboratory at the time of smear examination. For purposes of external quality assessment, a randomly selected 10% of isolates from each laboratory were required to be re-tested blindly by a superior laboratory.

2.4. Data inclusion and definitions

A patient with at least 2 positive sputum samples, or 1 positive sputum sample and abnormal chest radiograph/1 positive sputum culture was diagnosed as smear-positive PTB. The diagnosis of smear-negative PTB predominantly relied on clinical symptoms (cough for >2 weeks, fever for >2 weeks, weight loss, hemoptysis, etc) together with abnormal chest radiograph, the results of bacterial culture, and the effect of anti-TB treatment, and so on.[12] As HIV-associated TB may not have a major effect on the overall reduction in TB prevalence,[13,14] all PTB cases except those who have HIV co-infection (in China, HIV-positive patients are immediately transferred to HIV-specialized hospitals) were included in this study.

New case was the one who had never been treated for TB or had taken anti-TB drugs for <1 month. Among patients with cured or treatment completed outcomes, the one who was diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection) was relapsed case.[15]

2.5. Statistical analyses

Categorical variables (sex, race, stratum, geographic location, patients type [smear-positive PTB or smear-negative PTB], TB contact history, and prior TB treatment history) were summarized as proportions; continuous variables (age) were summarized with mean and standard deviation (SD). Categorical variables were compared by Pearson chi-square test or Fisher exact test.

We estimated the incidence rate per 100,000 people as the number of annual PTB cases divided by the annual population size. The overall incidence, the incidence stratified by sex, age group, treatment history, patients type, and geographical location were calculated. The joinpoint regression model[16] was used to examine incidence trends during 2005 to 2017. In this model, the trends were described by annual percent changes (APCs). The APCs were estimated by fitting a simple linear model on logarithm of rates regressed on time. The Z test was used to assess whether an APC was significantly different from 0. A nonsignificant ($P \geq .05$) APC was described as stable while a significant ($P < .05$) positive or negative APC was termed as increase or decrease.

All analyses were performed using SPSS software (version 17.0) and Joinpoint (version 4.3.1).

3. Results

3.1. Case estimates and characteristics

In the study period, 224,480 cases with PTB were identified in 6 cities of Shandong. The average age of these patients was 47.60 years with SD 19.62. Only 2.48% patients aged <18 years. Nearly all patients (99.62%) were Han, 70.82% were male and 93.23% were rural residents. Among all PTB patients, 116 744 (52.01%) were smear-positive PTB, whereas 107,736 (47.99%) were smear-negative PTB. The proportion of patients with TB contact history was 13.13%. A total of 205,716 (91.64%) cases were new cases and 18,764 (8.36%) were relapsed cases. In new cases, the proportions of smear-positive PTB and smear-negative PTB were nearly half and half (48.04% vs 51.96%). While the corresponding proportions were 95.45% and 4.55% in relapse cases (Table 1).

Figure 1 illustrates the distribution of averaged PTB incidence in 6 cities of Shandong, China 2005 to 2017. The averaged PTB incidence of the highest TB burden city (Linyi, 49.07 per 100,000) was 1.64 times of the incidence of the lowest TB burden city (Weifang, 29.90 per 100,000).

Table 1

Sociodemographic and clinical characteristics of 224,480 pulmonary tuberculosis patients in Shandong, China, 2005–2017.

Characteristics	New case		Relapse case			
	Smear-positive PTB n (%)	Smear-negative PTB n (%)	Smear-positive PTB n (%)	Smear-negative PTB n (%)	Total n (%)	*P*-value
Total	98,833 (44.03)	106,883 (47.61)	17911 (7.98)	853 (0.38)	224,480	
Stratum						
Urban	5863 (5.93)	8568 (8.02)	710 (3.96)	54 (6.33)	15195 (6.77)	
Rural	92,970 (94.07)	98,315 (91.98)	17,201 (96.04)	799 (93.67)	209,285 (93.23)	<.001
Ethnic group						
Han	98,526 (99.69)	106,389 (99.54)	17,862 (99.73)	851 (99.77)	223,628 (99.62)	
Other	307 (0.31)	494 (0.46)	49 (0.27)	2 (0.23)	852 (0.38)	<.001
Sex						
Male	71,063 (71.90)	73,559 (68.82)	13,734 (76.68)	614 (71.98)	158,970 (70.82)	
Female	27,770 (28.10)	33,324 (31.18)	4177 (23.32)	239 (28.02)	65,510 (29.18)	<.001
Age group, yr						
<18	2108 (2.13)	3382 (3.16)	71 (0.40)	11 (1.29)	5572 (2.48)	
18–34	27,933 (28.26)	35,714 (33.41)	2406 (13.43)	190 (22.27)	66,243 (29.51)	
35–60	37,886 (38.33)	38,389 (35.92)	7593 (43.39)	314 (36.81)	84,182 (37.50)	
>60	30,906 (31.27)	29,398 (27.50)	7841 (43.78)	338 (39.62)	68,483 (30.51)	<.001
TB contract history	8847 (8.95)	19,803 (18.53)	740 (4.13)	74 (8.68)	29,464 (13.13)	<.001
Geographical location						
Jinan	10,442 (10.57)	12,547 (11.74)	1161 (6.48)	18 (2.11)	24,168 (10.77)	
Dezhou	15,441 (15.62)	10,073 (9.42)	3241 (18.10)	230 (26.96)	28,985 (12.91)	
Jining	18,269 (18.48)	15,726 (14.71)	4131 (23.06)	74 (8.68)	38,200 (17.02)	
Linyi	27,305 (27.63)	36,077 (33.75)	5143 (28.71)	229 (26.85)	68,754 (30.63)	
Weifang	16,329 (16.52)	15,313 (14.33)	2363 (13.19)	85 (9.96)	34,090 (15.19)	
Yantai	11,047 (11.18)	17,147 (16.04)	1872 (10.45)	217 (25.44)	30,283 (13.49)	<.001

PTB = pulmonary tuberculosis.

3.2. Incidence rate

From 2005 to 2017, the incidence rate of smear-positive PTB (33.23 to 6.41 per 100,000) and relapse cases (5.11 to 1.01 per 100,000) decreased by about 80%, and the incidence rate of overall PTB (40.80 to 26.39 per 100,000) declined by 35.31%. The joinpoint regression indicated an APC of 3.5% ($P<.05$) during 2005–2008, −4.7% ($P<.05$) during 2008 to 2013; and −7.4% ($P<.05$) during 2013 to 2017 for overall PTB. The incidence rapidly decreased by 18.3% ($P<.05$) annually for smear-positive PTB during 2009 to 2017, and by 20.3% ($P<.05$) annually for relapse cases during 2010 to 2017. From 2005 to 2014, the incidence rate of smear-negative PTB increased from 7.57 to 24.21 per 100,000 (APC=26.2%, during 2005–2008 [$P<.05$]; APC=8.2%, during 2008–2004 [$P<.05$]). Then it remained at a stable level with a lower annual declining rate during 2014 to 2017 (APC=−7.4%, $P=.10$) (Tables 2 and 3).

The incidence stratified by sex, age, and geographical location also declined during the 13-year period. These changes in incidence stratified by sex were similar with that in overall PTB which were increased during 2005 to 2008 ($P<.05$) and decreased during 2008 to 2017 ($P<.05$). The highest incidence rate grouping by age was 92.81 per 100,000 among patients aged >60 years in 2005. The incidence in this age group of patients decreased in the following years reaching 45.84 per 100,000 in 2017. The largest decline in incidence grouping by geographical location occurred in Dezhou, dropped by 60.08% from 49.78 to 19.87 per 100,000. The smallest decline in incidence grouping by geographical location occurred in Weifang, dropped by 12.17% from 28.9 to 25.39 per 100,000 (Tables 2 and 3).

4. Discussion

This retrospective cohort review of PTB in the second largest province of China describes the characteristics and the epidemiology of PTB from 2005 to 2017. The major findings of this study are as follows:

(1) the incidence rate of overall PTB declined from 40.80 to 26.39 per 100,000 in the past 13 years;
(2) except smear-negative PTB (7.57 to 19.87 per 100,000), the incidence of smear-positive PTB and all that stratified by age, sex, and treatment history decreased;
(3) a regional disparity in incidence within the province was illustrated.

To accelerate the national TB control efforts, several strategies were implemented after 2000. First, the government expanded the DOTS programme nationwide, providing free treatment policy to all patients with active PTB.[5] Second, after the epidemic of SARS was brought under control, the stagnated TB control activities picked up rapidly, with increased public-health funding (reaching $36 million for TB in 2005), revised laws on TB control,[7] introduced internet-based disease reporting system,[8] and rebuilt local public-health facilities.[5] Third, free treatment for people with smear-negative PTB was available in 2005 for the first time.

With these strategies, the new smear-positive PTB cases handled by the DOTS programme increased to 80% till 2005 in China.[5] This study demonstrated that the incidence of overall PTB decreased 35.31% in 13 years. Before 2014, this reduction can be directly linked to the decrease among smear-positive PTB,

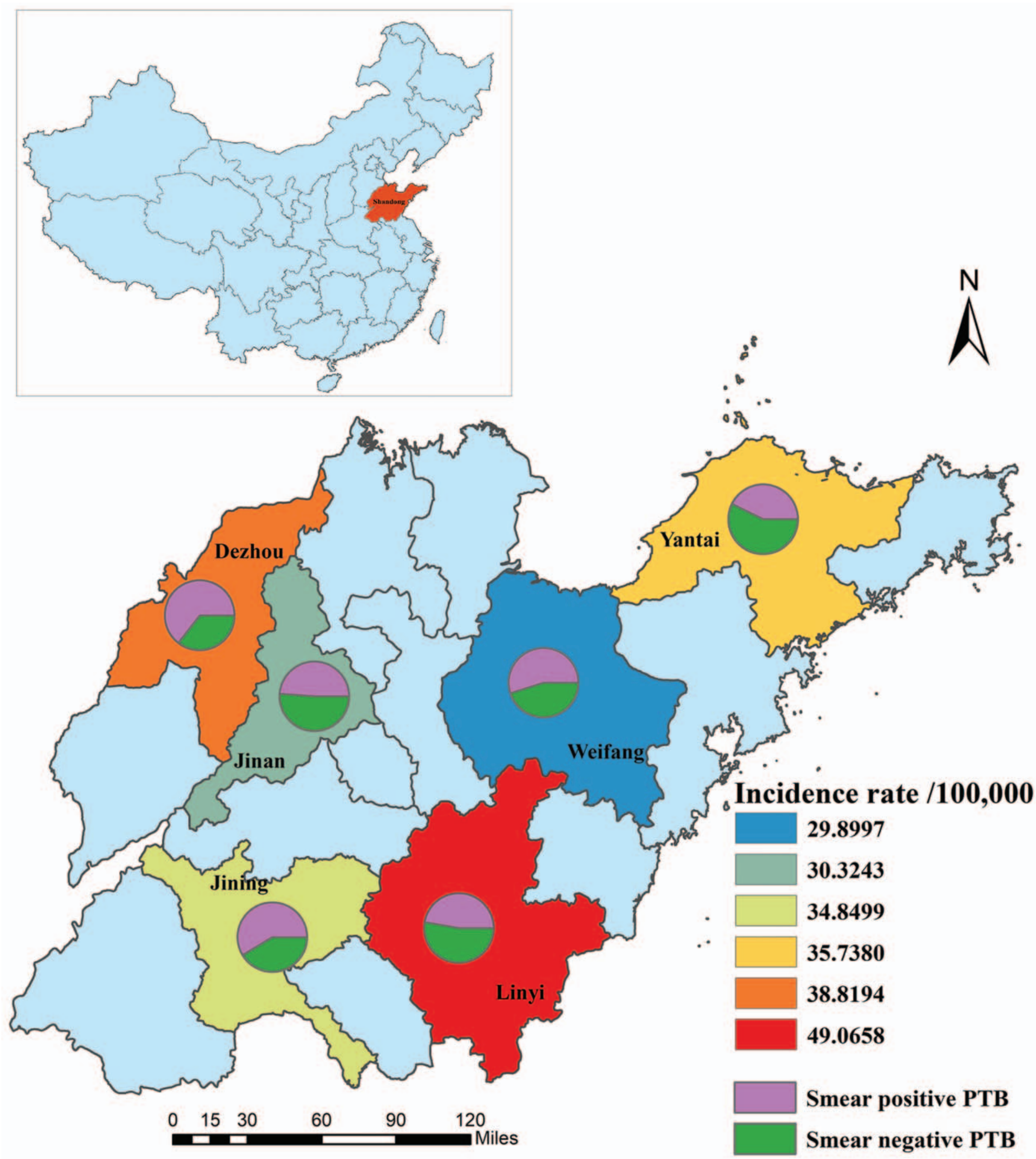

Figure 1. Averaged incidence of pulmonary tuberculosis in Shandong, China, 2005 to 2017. PTB=pulmonary tuberculosis.

as the incidence of smear-negative PTB start to decline after 2014. Without these strategies, most patients would have poor-quality DOTS services in some areas and inappropriate treatment in parts of the hospital system, even more patients would being undetected and malpractice.[9]

This study sheds light on how the country can further reduce its TB burden. First, the disease burden gradually shifted from smear-positive PTB to smear-negative PTB. Present TB control programs have led to a successful decline in the incidence of smear-positive PTB (33.23 to 6.41 per 100,000). Under the high population coverage of DOTS implemented by the CDC system through its local public health clinics, these patients are not likely to be a major driver of overall TB incidence in future.

The incidence rate of smear-negative PTB increased dramatically from 2005 to 2014, similar with previous research in China (31.86 to 39.28 per 100,000).[17] Due to the lack of bacteriological indicators, the diagnose of smear-negative PTB was more complicated than smear-positive PTB. The free treatment policy (in 2005), the development of modern technologies including interferon-γ release test (from 2010 in China), GeneXpert MTB/

Table 2

Incidence of pulmonary tuberculosis in Shandong, China, 2005–2017.

	Incidence per 100,000 population													Change* (%)
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2005–2017
Total	40.80	41.85	43.55	45.55	43.42	41.40	37.78	37.31	36.03	33.26	30.94	27.55	26.39	–35.31%
Sex														
Male	56.28	57.50	60.33	62.77	60.10	57.98	52.83	52.54	50.70	46.56	44.22	38.83	37.19	–33.92%
Female	24.86	25.75	26.31	27.88	26.29	24.33	22.28	21.60	20.91	19.50	17.20	15.89	15.23	–38.73%
Age groups, yr														
<18	7.70	6.72	6.39	4.93	5.41	3.72	3.93	4.04	4.60	4.75	4.50	3.58	3.77	–51.08%
18–34	41.04	44.42	46.20	51.60	49.40	48.40	44.71	43.31	42.65	40.79	36.70	34.82	33.42	–18.55%
35–60	40.84	41.32	40.83	42.56	41.08	39.93	36.48	36.16	34.51	31.79	29.13	25.60	24.48	–40.07%
>60	92.81	87.23	92.14	91.01	82.01	76.31	67.18	66.61	62.34	55.91	53.88	46.77	45.84	–50.61%
Patients type														
Smear-positive PTB	33.23	32.59	30.51	29.34	27.45	25.30	18.46	14.39	13.09	9.06	7.81	7.14	6.41	–80.72%
Smear-negative PTB	7.57	9.25	13.04	16.21	15.97	16.10	19.32	22.92	22.94	24.21	23.13	20.41	19.98	164.13%
Treatment history														
New case	35.69	37.26	38.93	40.74	38.85	37.22	34.34	34.85	33.78	31.81	29.65	26.42	25.38	–28.89%
Relapse case	5.11	4.58	4.62	4.81	4.58	4.18	3.45	2.47	2.25	1.45	1.29	1.13	1.01	–80.24%
Geographical location														
Jinan	29.12	29.32	31.79	34.82	32.24	31.77	28.95	32.19	31.95	30.32	29.13	27.50	25.56	–12.24%
Dezhou	49.78	50.32	49.87	52.78	47.98	39.93	39.88	38.41	36.58	30.40	28.91	22.85	19.87	–60.08%
Jining	43.76	42.93	43.97	44.07	42.19	42.15	34.70	33.73	30.38	28.65	25.48	22.94	20.95	–52.13%
Linyi	56.19	54.34	58.61	59.26	58.06	53.70	49.87	47.95	48.16	43.61	41.23	35.75	35.33	–37.13%
Weifang	28.90	32.22	32.36	34.80	32.24	33.43	29.94	29.63	30.17	29.65	26.41	24.14	25.39	–12.17%
Yaitai	31.65	37.86	39.48	43.58	42.88	41.05	38.66	38.46	34.38	31.97	30.26	28.44	26.00	–17.84%

PTB = pulmonary tuberculosis.

* The % changes were calculated as follows: (incidence in 2017 – incidence in 2005)/incidence in 2005.

Table 3

Annual percentage change in incidence of pulmonary tuberculosis in Shandong, China, 2005–2017.

	Period	Trend	APC (95% CI)	*P*-value
Overall PTB	2005–2008	Increase	3.5 (0.2, 6.9)	<.05
	2008–2013	Decrease	–4.7 (–6.7, –2.7)	<.05
	2013–2017	Decrease	–7.4 (–9.6, –5.2)	<.05
Sex				
Male	2005–2008	Stable	3.6 (–0.3, 7.7)	.10
	2008–2013	Decrease	–4.3 (–6.6, –1.9)	<.05
	2013–2017	Decrease	–7.4 (–10.0, –4.8)	<.05
Female	2005–2008	Stable	3.8 (–0.0, 7.8)	.10
	2008–2017	Decrease	–6.4 (–7.1, –5.7)	<.05
Age group (years)				
<18	2005–2010	Decrease	–14.2 (–19.3, –8.9)	<.05
	2010–2017	Stable	–0.0 (–4.5, 4.7)	1.00
18–34	2005–2008	Increase	8.2 (4.3, 12.2)	<.05
	2008–2017	Decrease	–4.6 (–5.2, –3.9)	<.05
35–60	2005–2008	Stable	1.5 (–2.1, 5.2)	.30
	2008–2013	Decrease	–4.0 (–6.2, –1.8)	<.05
	2013–2017	Decrease	–8.6 (–11.1, –6.1)	<.05
>60	2005–2008	Stable	–0.8 (–5.5, 4.2)	.70
	2008–2017	Decrease	–7.3 (–8.2, –6.4)	<.05
Patients type				
Smear-positive PTB	2005–2009	Stable	–4.2 (–9.1, 0.9)	.10
	2009-2017	Decrease	–18.3 (–20.6, –15.9)	<.05
Smear-negative PTB	2005–2008	Increase	26.2 (9.3, 45.8)	<.05
	2008–2014	Increase	8.2 (3.3, 13.2)	<.05
	2014–2017	Stable	–7.4 (–15.7, 1.8)	.10
Treatment history				
New case	2005–2008	Stable	3.9 (–0.3, 8.4)	.10
	2008–2014	Decrease	–3.9 (–5.7, –2.1)	<.05
	2014–2017	Decrease	–7.7 (–11.9, –3.2)	<.05
Relapse case	2005–2010	Stable	–3.2 (–7.1, 0.8)	.10
	2010–2017	Decrease	–20.3 (–23.4, –17.1)	<.05

APC = annual percent change, PTB = pulmonary tuberculosis.

RIF sputum test (from 2010), adenosine deaminase, and TB antibody test (in 2008), the shortening time of diagnostic delays and treatment delays, the specialist training, the updated diagnostic criteria (in 2008), and so on, all these factors could influence the identification of smear-negative PTB.[17,18] Moreover, as a low-income country, whether to perform the expensive modern technologies based on the laboratory level and the patients' economic condition in China. Thus we speculated that the gradually increased incidence for smear-negative PTB before 2014 was a combined results of all these factors in this study.

Although it is deemed that smear-negative PTB which account for 42% of PTB were less infectious, still 20% of TB transmission was caused by these patients.[19] Moreover, without treatment an estimated 70% of suspected smear-negative TB patients progressed to active disease in a year follow-up.[20] With the disease burden shifted, more quick and accurate diagnostic among suspected patients especially among bacterium negative patients is vital.

Second, the burden of new cases remains heavily. New infection and new case of disease stand for the transmission of TB.[21] In China, due to the limited resource, the current case-finding strategy mainly relies on passive case-finding, waiting for the symptomatic individuals voluntarily seeking medical care and treatment. One study in rural China revealed that passive strategy could detect only a quarter of total TB cases compared with active case-finding strategies.[22] What worse a third of TB suspects in China's rural settings do not seek care after 3 weeks of persistent cough.[23] In our study, about 93% patients lived in rural areas. The lager amount of undetected and delayed case (delay in seeking medical service,[24] delay in obtaining diagnosis,[25] and delay in receiving treatment[26]) played a vital role in TB transmission. Earlier case detection and prompt initiation of effective treatment to rapidly render the source patients non-infectious is crucial to reduce TB transmission.

Third, increased focus should be placed on old population, the latent reservoir who contribute incidence due to endogenous reactivation.[27] Previous study demonstrated that chronic comorbidities, malignancy, malnutrition, excess alcohol use, and the waning immunity predisposes the ageing patient to infections disease such as TB.[28] In patients aged ≥60 years, about 90% of TB cases are due to reactivation of primary infection.[29] What worse, people in this population group is expected to rise to about 22% by 2050.[30] In our study, patients aged >60 years accounted for 30.51% of all PTB patients, the highest incidence rate grouping by age was 92.81 per 100,000 among this age group in 2005. The DOTS strategy, which does not specifically address reactivation disease in the short term seems to be limited. One study of TB transmission through an individual-based computational model reported that maintenance of the DOTS strategy only will hardly achieve the 2035 targets. While along with other feasible interventions and preventative therapy for elders would enable China to nearly reach both the 2035 incidence and mortality goal.[27] As elderly TB patients are less likely to be smear positive, more likely to default/die, and more common to have adverse events to anti-TB drugs,[31] appropriate interventions are urgently needed for effective management of TB in this vulnerable population.

Forth, regional disparities are one of the challenges facing TB control in China. The China's Fifth National TB Epidemiological Survey in 2010 elucidated that the prevalence of bacteriologically confirmed PTB in the western region (212 per 100,000) was 1.7 times of that in the central region (124 per 100,000), and 3.2 times of that in the eastern region (66 per 100,000). Consistent with previous research, our study demonstrates a regional disparity of PTB within Shandong province.[32] Medical factors, income, education, geography, environment, customs, and so on were associated with TB prevalence.[28] Regional equity both within and across province is essential for future TB control.

This study had some limitations. First, as a retrospective study, few information on incomes, expenditure, complications, living conditions, and the specific diagnostic methods for every smear-negative PTB were provided by the medical records. Second, all information was obtained from Information System for Disease Control and Prevention, in which primary information may have detection bias under different discretion of the treating physician and be vague and was re-evaluated by trained research coordinators. Last, because only 1 province on the eastern coast of China was examined, the economic and regional disparities limited the generalizability of the results.[28]

In conclusion, the incidence of PTB in Shandong Province, China, decreased over the study periods. With persistent efforts to combat TB, the burden of TB has shifted. While further reducing the level of smear-positive PTB and relapse cases may have a modest effect on TB control, additional efforts in reducing the incidence of smear-negative PTB and elderly patients may have a greater impact on future TB control.

Although China has achieved the 2015 global TB control goal,[5] still a million incident TB cases are reported annually.[1] With TB burden shifting, China still faces huge challenges to reach the 2035 goal.[27] Understanding the long-term trends and distribution of TB can shed light on future TB control programs in China, thereby contributing to the realization of the end TB strategy.

Acknowledgments

We would like to express our deep appreciation to all the individuals who contributed to this work.

Author contributions

LHC, GH, and TNN planned the research, developed the protocol, and implemented the survey. LYF, LJY, and SWM collected data, constructed the figures and tables. WSS, LYX, and LY analyzed and interpreted data. TNN wrote the first draft of the report. All authors critically reviewed the report and approved the final version.

Conceptualization: Yi-Fan Li, Jin-Yue Liu, Wan-Mei Song.
Data curation: Shan-Shan Wang, Wan-Mei Song.
Formal analysis: Shan-Shan Wang.
Funding acquisition: Huai-Chen Li.
Investigation: Yao Liu.
Methodology: Yi-Fan Li, Yun-Xia Liu, Jin-Yue Liu, Yao Liu.
Project administration: Yun-Xia Liu.
Resources: Hong Geng.
Supervision: Hong Geng, Huai-Chen Li.
Validation: Huai-Chen Li.
Writing – original draft: Ning-Ning Tao.
Writing – review and editing: Ning-Ning Tao.

References

[1] World Health Organization. Global Tuberculosis Report 2018. Geneva: The Organization; 2018. WHO/CDS/TB/2018.20. Available at: https://www.who.int/tb/publications/global_report/en/. Accessed October 2, 2018.

[2] Lonnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. Lancet 2010;375:1814–29.
[3] China Tuberculosis Control CollaborationResults of directly observed short-course chemotherapy in 112 842 Chinese patients with smear-positive tuberculosis. Lancet 1996;347:358–62.
[4] Xianyi C, Fengzeng Z, Hongjin D, et al. The DOTS strategy in China: results and lessons after 10 years. Bull World Health Organ 2002;80:430–6.
[5] Wang L, Liu J, Chin DP. Progress in tuberculosis control and the evolving public-health system in China. Lancet 2007;369:691–66.
[6] China National Health Economics InstituteChina National Health Accounts Report. China National Health Economics Institute, Beijing:2005.
[7] State Council of the People's Republic of China. Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases. Available at: http://www.chinacdc.cn/n2722442/n272530/n272907/n272922/6837.html. Accessed January 5, 2007.
[8] Ma JQ, Yang GH, Shi XM. Information technology platform in China's disease surveillance system. Dis Surveill 2006;21:1–3.
[9] Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990–2010; a longitudinal analysis of national survey data. Lancet 2014;383:2057–64.
[10] China Tuberculosis Control CollaborationThe effect of tuberculosis control in China. Lancet 2004;364:417–22.
[11] Ukwaja KN, Modebe O, Igwenyi C, et al. The economic burden of tuberculosis care for patients and households in Africa: a systematic review. Int J Tuberc Lung Dis 2012;16:733–9.
[12] National Health and Family Planning Commission of the People's Republic of China. The Diagnostic Criteria of PTB in China (WS288-2008). Available at: http://www.nhfpc.gov.cn/zhuz/s9491/200801/38801.shtml. Accessed January 5, 2017.
[13] UNAIDS. 2012 China AIDS Response Progress Report. Available at: http://unaids.org.cn/pics/20120614140133.pdf. Accessed December 1, 2013.
[14] Wu Z, Sullivan SG, Wang Y, et al. Evolution of China's response to HIV/AIDS. Lancet 2007;369:679–90.
[15] World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis, 5th ed. Geneva: The Organization; 2015. WHO/HTM/TB/2015.13. Available at: http://apps.who.int/bookorders/WHP/dartprt1.jsp?sesslan=1&codlan=1&codcol=93&codcch=319. Accessed August 28, 2018.
[16] Shigui Y, Jie W, Cheng D, et al. Epidemiological features of and changes in incidence of infectious diseases in China in the first decade after the SARS outbreak: an observational trend study. Lancet Infect Dis 2017;17:716–25.
[17] Huang F, Liu E, Xia Y, et al. The analysis of national smear negative pulmonary tuberculosis incidence and mortality, 2005–2014. Chin J Antituberc 2015;37:473–7.
[18] Li G, Chen X. Progress in laboratory diagnosis of smear-negative pulmonary tuberculosis. J Chin Physician 2010;12:142–4.
[19] Behr MA, Warren SA, Salamon H, et al. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. Lancet 1999;353:444–9.
[20] Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Research CouncilA study of the characters and course of sputum smear negative pulmonary tuberculosis. Tubercle 1981;62:155–67.
[21] Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompteffective treatment. Lancet 2015;386:2334–43.
[22] Liao P, Guo M, Tang F, et al. Analysis of patients from active case finding in rural areas of Wusheng, Sichuan. Chin J Antituberculosis (Zhongguo Fang Lao Za Zhi) 2016;38:576–81.
[23] Zhang T, Tang S, Jun G, et al. Persistent problems of access to appropriate, affordable TB services in rural China: experiences of different socio-economic groups. BMC Publ Health 2007;7:19.
[24] Rajeswari R, Chandrasekaran V, Suhadev M, et al. Factors associated with patient and health system delays in the diagnosis of tuberculosis in South India. Int J Tuberc Lung Dis 2002;6:789–95.
[25] Chang CT, Esterman A. Diagnostic delay among pulmonary tuberculosis patients in Sarawak, Malaysia: a cross-sectional study. Rural Remote Health 2007;7:667.
[26] Zerbini E, Chirico MC, Salvadores B, et al. Delay in tuberculosis diagnosis and treatment in four provinces of Argentina. Int J Tuberc Lung Dis 2008;12:63–8.
[27] Huynh GH, Klein DJ, Chin DP, et al. Tuberculosis control strategies to reach the 2035 global targets in China: the role of changing demographics and reactivation disease. BMC Med 2015;13:88.
[28] Mijiti P, Yuehua L, Feng X, et al. Prevalence of pulmonary tuberculosis in western China in 2010–11: a population-based, cross-sectional survey. Lancet Glob Health 2016;4:e485–494.
[29] Yoshikawa TT. Tuberculosis in ageing adults. J Am Geriatr Geriatr Soc 1992;40:178–87.
[30] Media Centre, United Nations of Population Fund, Ageing. Available at: http://www.unfpa.org/ageing. Accessed July 20, 2016.
[31] Velayutham BR, Nair D, Chandrasekaran V, et al. Profile and response to anti-tuberculosis treatment among elderly tuberculosis patients treatedunder the TB Control programme in South India. PLoS One 2014;11:e88045.
[32] Li YW, Chen J, Wang H, et al. Spatial-temporal analysis of pulmonary tuberculosis in Shandong province. Chin J Epidemiol 2016;37:1257–61.