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ORIGINAL RESEARCH

Trends in the Notification Rates and Treatment Outcome of Tuberculosis in Shandong Province, China, 2005–2021

Qilin Han[1,2], Yifan Li[3], Yao Liu[1], Xuehan Zhu[1], Qiqi An[4], Yameng Li[5], Tingting Wang[5], Yuzhen Zhang[1,2], Yingying Li[5], Weiwei Fang[1,2], Ningning Tao[1,*], Huaichen Li[1,2,*]

[1]Department of Pulmonary and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China; [2]Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong, 250117, People's Republic of China; [3]Department of Pulmonary and Critical Care Medicine, The Third Affiliated Hospital of Shandong First Medical University (Affiliated Hospital of Shandong Academy of Medical Sciences), Jinan, Shandong, 250031, People's Republic of China; [4]Department of Pulmonary and Critical Care Medicine, Xingyi People's Hospital, Qianxinan, Guizhou, 561499, People's Republic of China; [5]Shandong University of Traditional Chinese Medicine, Jinan, Shandong, 250355, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ningning Tao, Department of Pulmonary and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, People's Republic of China, Email 826794467@qq.com; Huaichen Li, Department of Respiratory and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324 Jingwuweiqi Road, Huaiyin District, Jinan, Shandong, 250021, People's Republic of China, Email lihuaichen@163.com

Purpose: To analyze the time trends in the notification rates of registered tuberculosis (TB) and bacteriologically confirmed TB in Shandong Province. And analyze the changes in TB treatment outcomes during 2005–2021.

Patients and Methods: The information of TB patients registered in the Shandong Information Center for Disease Control and Prevention (CDC) was collected during 2005–2021. We calculated the notification rates of registered TB and bacteriologically confirmed TB. Moreover, we calculated the year-to-year change rate of TB in treatment outcomes before and after COVID-19. The time trends were analyzed using the joinpoint regression method and illustrated as the annual percentage change (APC) of notification rates.

Results: A total of 236,898 cases of TB were diagnosed during 2005–2021, of which 51.11% were bacteriologically confirmed cases. Since 2008, the notification rates of registered TB have declined. The notification rates of bacteriologically confirmed TB had been declining during 2005–2016, then remained stable after 2016. In subgroup, the notification rates of both registered TB and bacteriologically confirmed TB were higher among men, rural residents, and people aged ≥ 60 years. Compared with clinically confirmed TB, bacteriologically confirmed TB has shown higher rates of poor outcomes since 2008 and higher case fatality rate since 2005. The rate of poor outcomes remained stable during 2008–2019. However, after the COVID-19 outbreak, the rate of poor outcomes and case fatality rate of TB has risen significantly.

Conclusion: After unremitting efforts to fight against TB, the notification rates of registered TB and bacteriologically confirmed TB declined in Shandong Province. The rate of poor outcomes remained stable during 2008–2019, then rise significantly after the COVID-19 outbreak. In the context of the long-term existence of COVID-19, further efforts should be made in TB diagnosis and treatment among high-risk population, especially with regard to males, rural residents and older adults.

Keywords: tuberculosis, joinpoint regression, time trends, COVID-19

Introduction

Tuberculosis (TB) is caused by the bacteria Mycobacterium tuberculosis (M. tb), which can be spread by respiratory droplets or aerosols, and infect its only host human beings. Bacteriologically confirmed TB including sputum smear positive, culture-positive and molecular test positive are more likely to spread M. tb and undergo TB-associated death.[1–3]

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The identification and management of bacteriologically confirmed TB cases are vital for TB control. Before the COVID-19 pandemic, TB not only ranked among the top ten causes of mortality worldwide but also stood as the most perilous infectious disease, surpassing human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS).[4] About 10.6 million new cases of active TB were reported by World Health Organization (WHO) in 2022. Ranking third after India and Indonesia, China accounts for 7.1% of TB cases. In 2022, TB infection led to 1.3 million deaths.[5]

Before the WHO introduced the Directly Observed Therapy, Short Course (DOTS) Strategy in 1995, China had already adopted DOTS in 13 provinces (including Shandong Province) which housed about half of the nation's population.[6] By 2005, the DOTS program had been extended to the entire nation. The frequency of pulmonary tuberculosis (PTB) in China dropped from 611 per 100,000 in 1990 to 442 per 100,000 in 2010 as a result of the DOTS strategy and other TB control measures. Moreover, the prevalence of bacteriologically confirmed PTB also dramatically decreased during this period.[7] China still has a long and difficult way in TB control, even with the advancements made. Particularly since the pandemic of COVID-19 in 2019, the vast majority of medical resources focus on the control of COVID-19, which making the management of TB even more difficult.[8] A previous study found that TB treatment coverage fell by 11% during the pandemic.[9] A study in North America found a 49.8% decline in the rates of TB treatment success (TB cure or treatment completion) during the pandemic compared to before.[10] There was also a significant increase in the proportion of poor outcomes of TB treatment during the COVID-19 pandemic.[11–13] In fact, it is estimated that the COVID-19 pandemic would cause a 20% rise in TB-related mortality over the next five years worldwide.[14] This global health threat poses a significant risk to health security.

Around the world, time trends in TB notification vary due to different national policies to control TB. A study conducted in India found a significant decrease in notification between 1990 and 2019.[15] According to a Brazilian study, the notification rates of TB showed different trends between 2001 and 2017 which began with higher numbers, suffered a decrease, and ended in an increase.[16] The Singapore study reported that the notification rates of TB experienced a similar pattern during 1998-2008.[17] Previous studies had analyzed the epidemiological characteristics of PTB in Shandong.[18] However, few studies aimed to explore time trends in the notification rates of registered TB and impact of COVID-19 outbreaks on TB treatment outcomes. The current study intended to apply joinpoint regression to analyze the time trends in the notification rates of registered TB cases and bacteriologically confirmed TB cases at the provincial level during 2005–2021, this study also calculated the year-to-year change rate of treatment outcomes before and after the COVID-19.

Methods

Data Source

This study was conducted in Shandong which is the second most populous province in China. At the time of the 2020 Census, Shandong had 101.5 million people living in 17 municipalities and 140 counties (districts). Data of TB patients from Jan 1, 2005 to Dec 31, 2021 were extracted from the Shandong Information Center for Disease Control and Prevention (CDC). The CDC has been keeping track of TB patients with demographics, diagnoses, treatments, and outcomes in Shandong Province since 2005. Once diagnosed with TB, the case must be reported to the CDC and recorded in a database within 24 hours, otherwise they will be deemed as illegal. Taking into account practicality, medical service level and TB burdens, we gathered all TB cases in six Shandong province cities, including Jinan, Yantai, Linyi, Dezhou, Jining and Liaocheng. From 2005 to 2021, demographic data were collected from the Shandong Statistical Yearbook.[19]

In this study, the details of TB cases including demographic information (sex, age, and residence and population mobility), clinical characteristics (bacteriology results, infection site, TB treatment history, and treatment outcomes) were acquired from the database. Patients with a bacteriological or clinical diagnosis of TB were included in the study. Patients change diagnosis during treatment and patients with missing key information were excluded from the analysis. Bacteriologically confirmed TB including sputum smear positive or culture-positive or molecular test positive. In addition, clinically confirmed TB was diagnosed in strict accordance with the clinical diagnosis guidelines and with the consultation and discussion of at least three chief physicians. Information refering to individual privacy including names, identifying numbers, and contact details were deleted. Annual sex and age-specific population were calculated based on the specific ratio according to the sixth national census of China in 2010. The National Bureau of Statistics of China provided the population data for the Sixth National Census in 2010.

Case Definitions

According to the WHO Definitions and reporting framework for TB,[20] we use the following definitions: A clinically diagnosed TB case is one that does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. New cases have never been treated for TB or have taken anti-TB drugs for less than 1 month. Relapse cases have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection). Treatment success was the sum of cured and treatment completed. Cured referred to a patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion. Treatment completed is defined as a TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results were unavailable. Poor outcomes include treatment failed, died, lost to follow-up and not being evaluated. Treatment failed: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment. Died: A TB patient who dies for any reason before starting or during the course of treatment. Lost to follow-up: A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more. Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases transferred out to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit. The floating population is defined as individuals who have resided at the place of destination for at least six months without local household registration status.[21] In this study, we define those who cross county boundaries and up to standard as floating population.

Statistical Analysis

We calculated the annual notification rates of registered TB cases and bacteriologically confirmed cases per 100,000 people in Shandong Province. Moreover, based on this information, we divide the cases into different subgroups such as sex, age group, treatment history, population mobility and patient residence. In addition to calculated overall notification rates, notification rates of subgroups were also calculated. In this study, we used the joinpoint regression methods to evaluate the time trends and APC of notification rates and its significance. Grid search method (GSM) is an acquiescent method for the model modeling and Monte Carlo permutation testing is an acquiescent method for the model optimization. The Bayesian information criterion (BIC) was used to adjust the statistical significance level.[22] Finally, the above method is used to select the best connection point of the interval function. In joinpoint regression model analysis, the primary indicators for characterizing time trend changes are APC and 95% confidence interval (CI). We provided the APC and 95% CI for each section. In the joinpoint regression model, the temporal variation was described by the following two terms: increase (APC > 0, $p<0.05$); decrease (APC < 0, $p<0.05$). When the 95% CI for APC did not contain zero ($P < 0.05$), they were deemed significant. Additionally, in order to assess the curative effect of notified TB cases and bacteriologically confirmed TB cases therapy and the impact of COVID-19 outbreak on TB treatment in Shandong Province, we separately calculated the year-to-year changes of TB cases in treatment outcomes during 2005–2019 and 2019–2021. We classified the outcomes of the treatment into treatment success and poor outcomes. The year-to-year change rate of treatment success, poor outcomes and case fatality rate of TB were calculated respectively. The year-to-year change rate during 2005–2019 was calculated using the following calculation formula: $\sqrt[2008-2005]{\text{the incidence of2008}/\text{the incidence of2005}}\text{-1}$ and $\sqrt[2019-2008]{\text{the incidence of2019}/\text{the incidence of2008}}\text{-1}$. In a similar way, the calculation formula of year-to-year change rate during 2019–2021 is $\sqrt[2021-2019]{\text{the incidence of2021}/\text{the incidence of2019}}\text{-1}$. When the year-to-year change rate >0, it is defined as increase and when it <0, defined as decrease.

All analyses were performed using SPSS software (version 26.0, SPSS Inc, Chicago, IL, USA) and Joinpoint Desktop Software (version 4.9.1.0, National Cancer Institute, Bethesda, MD, USA).

Results

From 2005 to 2021, there were 236,898 notified TB cases in six cities of Shandong Province. The mean age of these patients was 48.18 years with standard deviation (SD) 19.49. About 69.93% of these cases were males, 34.08% aged ≥ 60 years, 7.91% relapse cases, and 79.61% rural residents. The majority of cases were PTB which accounting to 98.61% (Table 1). About half of the patients were bacteriologically confirmed to account for 51.10% (121,057).

In Shandong Province, the notification rates of registered TB cases dropped from 48.0 per 100,000 to 15.5 per 100,000 between 2005 and 2021. The APC were 1.9% (95% CI −2.3 to 6.3), −4.3% (95% CI −6.1 to −2.5), −7.6% (95% CI −15.9 to 1.4) and −16.6% (95% CI −23.8 to −8.6), respectively during 2005–2008, 2008–2014, 2014–2017, and 2017–2021 (Table 2 and Figure 1). The APC among male patients were −3.9% (95% CI −5.8 to −2.0) during 2008–2014, −7.7% (95% CI −16.4 to 1.9) during 2014–2017 and −18.2% (95% CI −25.9 to −9.8) during 2017–2021. The notification rates of registered TB had been trending and decreased in the last few years in all five age groups. The notification rates of relapse TB cases showing a clear downward trend, the APC were −4.5% (95% CI −7.8 to −1) and −21.6% (95% CI −24 to −19.2), respectively during 2005–2010 and 2010–2021. The notification rates of the floating population showed an upward trend during 2005–2009 and 2012–2018, the APC were 102.1% (95% CI 1.2 to 303.3) and 36.7% (95% CI 10.2 to 69.7), remained stable during 2009–2012 and 2018–2021. In rural residence, the APC were −2.6% (95% CI −3.8 to −1.4), −8.4% (95% CI −13.9 to −2.4) and −31.4% (95% CI −41.9 to −19.1), respectively during 2005–2013, 2013–2017 and 2017–2021 (Table 2 and Supplementary Figure S1).

The notification rates of bacteriologically confirmed TB cases showed different patterns. The notification rates of bacteriologically confirmed TB cases decreased significantly during 2005–2016, with notification rates dropping from

Table 1 Socio-Demographic and Clinical Characteristics of TB Cases in Shandong Province, 2005–2021

Variable	Frequency	Percentage (%)
Sex		
Male	165,656	69.93
Female	71,242	30.07
Age		
0–14	892	0.38
15–29	58,830	24.83
30–44	40,652	17.16
45–59	55,794	23.55
≥60	80,730	34.08
Treatment history		
New case	218,161	92.09
Relapse case	18,737	7.91
Residence		
Rural	188,584	79.61
Urban	48,314	20.39
Floating population		
No	217,273	91.72
Yes	19,625	8.28
Case definition		
Bacteriologically confirmed	121,057	51.10
Clinically confirmed	115,841	48.90
Type		
Pulmonary TB	233594	98.61
Extrapulmonary TB	3304	1.39
Treatment outcomes		
Treatment success	224,575	94.80
Poor outcomes	12,323	5.20

Table 2 Joinpoint Analysis in Notification Rates of Registered TB in Shandong Province, 2005–2021

	Year	Notification rates of registered TB case[a]	Annual percent change (95% CI)	P value
Overall	2005–2008	48.0–49.8	1.9(−2.3—6.3)	0.321
	2008–2014	49.8–37.3	−4.3(−6.1— −2.5)	0.001
	2014–2017	37.3–30.1	−7.6(−15.9—1.4)	0.084
	2017–2021	30.1–15.5	−16.6(−23.8— −8.6)	0.003
Sex				
Male	2005–2008	65.7–68.0	1.8(−2.6—6.5)	0.362
	2008–2014	68.0–52.1	−3.9(−5.8— −2)	0.003
	2014–2017	52.1–42.1	−7.7(−16.4—1.9)	0.096
	2017–2021	42.1–20.4	−18.2(−25.9— −9.8)	0.002
Female	2005–2008	29.8–31.2	2.6(−1.5—6.8)	0.186
	2008–2017	31.2–17.9	−5.7(−6.6— −4.8)	< 0.001
	2017–2021	17.9–10.5	−13.8(−20.7— −6.2)	0.003
Age				
0–14	2005–2021	2.1–0.6	−6.5(−9.6— −3.3)	0.001
15–29	2005–2008	50.0–58.1	6.2(4.4—8)	< 0.001
	2008–2014	58.1–39.8	−6.1(−6.8— −5.4)	< 0.001
	2014–2018	39.8–28.4	−10.1(−11.9— −8.3)	< 0.001
	2018–2021	28.4–12.2	−21.7(−26.5— −16.5)	< 0.001
30–44	2005–2010	35.2–32.0	−0.5(−3.4—2.5)	0.717
	2010–2021	32.0–13.3	−7.2(−8.7— −5.7)	< 0.001
45–59	2005–2013	53.5–44.6	−1.9(−3.4— −0.3)	0.021
	2013–2021	44.6–17.7	−10.4(−13.3— −7.4)	< 0.001
≥60	2005–2016	107.1–82.1	−2.3(−3.2— −1.4)	< 0.001
	2016–2021	82.1–36.9	−16.2(−21.7— −10.3)	< 0.001
Treatment history				
New case	2005–2008	41.9–44.6	2.3(−2.1—6.9)	0.251
	2008–2014	44.6–35.8	−3.2(−5— −1.3)	0.006
	2014–2017	35.8–29.3	−7(−15.3—2.1)	0.107
	2017–2021	29.3–15.1	−16.5(−23.7— −8.7)	0.003
Relapse case	2005–2010	6.1–4.4	−4.5(−7.8— −1)	0.015
	2010–2021	4.4–0.4	−21.6(−24— −19.2)	< 0.001
Floating population				
No	2005–2013	47.6–39.0	−2.4(−4.3— −0.5)	0.017
	2013–2021	39.0–11.9	−14.7(−18.6— −10.7)	< 0.001
Yes	2005–2009	0.3–3.4	102.1(1.2—303.3)	0.047
	2009–2012	3.4–1.9	−23.6(−73.3—118.1)	0.553
	2012–2018	1.9–11.2	36.7(10.2—69.7)	0.012
	2018–2021	11.2–3.7	−23.4(−65.1—68)	0.438
Residence				
Rural	2005–2013	40.1–32.4	−2.6(−3.8— −1.4)	0.001
	2013–2017	32.4–23.6	−8.4(−13.9— −2.4)	0.012
	2017–2021	23.6–6.5	−31.4(−41.9— −19.1)	0.001
Urban	2005–2008	7.3–10.2	10.9(−4.9—29.2)	0.162
	2008–2016	10.2–6.4	−5.4(−8.9— −1.6)	0.01
	2016–2021	6.4–9.0	10.8(0.1—22.7)	0.048

Notes: [a] The notification rates of registered TB cases at the first and the last year of the segment.

38.7 per 100,000 to 7.9 per 100,000. The APC were −6.3% (95% CI −8.7 to −4) and −20.2% (95% CI −23.2 to −17.2), respectively during 2005–2010 and 2010–2016. After 2016, it showed a relatively stable trend (APC=3.4%, 95% CI −4.3 to 11.8) (Table 3 and Figure 2). In males and females, the trends of notification rates in the bacteriologically confirmed

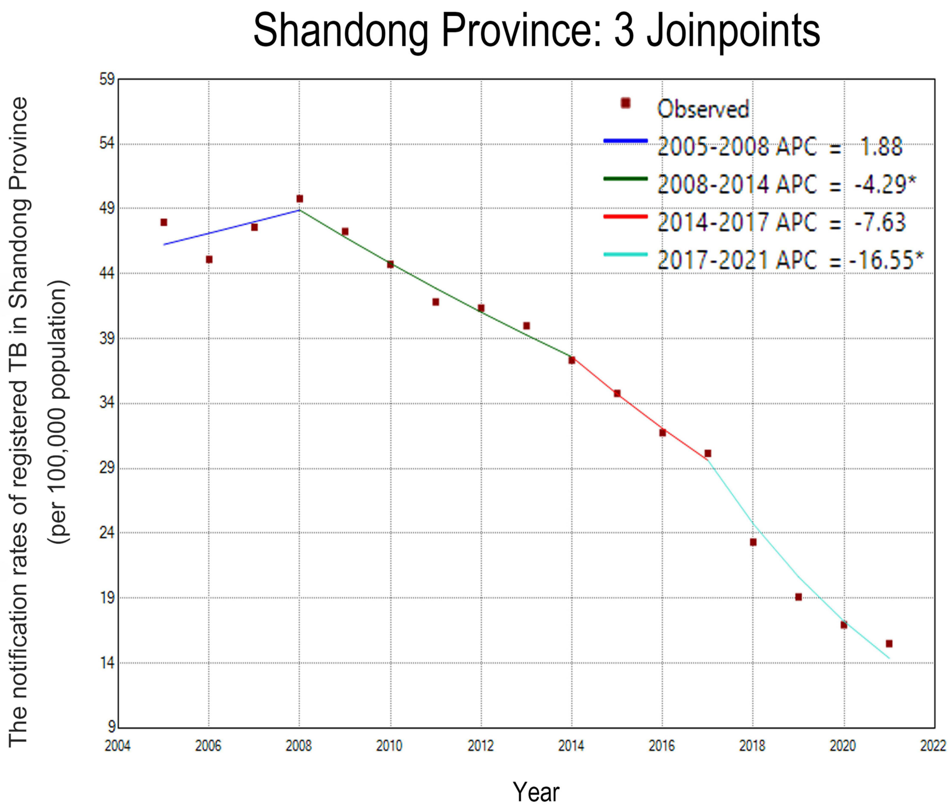

Figure 1 Change in notification rates of registered TB estimated by joinpoint model (solid line) in Shandong Province, 2005–2021. * $p<0.05$.

TB cases were the same as Shandong province. The notification rates of bacteriologically confirmed TB across different age groups showed different trends. Changes in the 0–14 age group showed a large difference, rates showed a downward trend during 2005–2014, the APC was −29.5% (95% CI −37.3 to −20.7). However, following that, the notification rates of this group showed a considerable rising trend, the APC was 37.0% (95% CI 0.5 to 86.7). The 30–44 age group also showed an increasing trend during 2016–2021, the APC was 12.5% (95% CI 1.7 to 24.3). Other age groups showed a downward trend before 2016 and since then remained stable. The notification rates of new cases decreased during 2005–2016, since then it has been steady. The notification rates of relapse cases had been decreasing since 2005. The floating population trend has changed significantly in the last few years, the APC were 89.9% (95% CI 28.8 to 180) during 2005–2009, −22.4% (95% CI −45.4 to 10.4) during 2009–2013 and 25.2% (95% CI 14 to 37.5) during 2013–2021. In rural residence, the notification rates of bacteriologically confirmed TB cases have been decreasing since 2005. In urban residence, the APC were −3.9% (95% CI −8.2 to 0.5) during 2005–2010 and −18.9% (95% CI −23.8 to −13.7) during 2010–2016. There was a noticeable increase of notification rates in the urban residence during 2016–2021, the APC was 34.1% (95% CI 22.3 to 47) (Table 3 and Supplementary Figure S2).

The rates of TB treatment outcomes remained stable during 2008–2019 (Table 4 and Figure 3). The rates of TB treatment success increased at an average rate of 0.01% per year during 2008–2019. The changes of treatment success rate in bacteriologically confirmed TB and clinically confirmed TB were consistent with the general trend (Figure 3A). The rates of poor outcomes dropped at a rate of 2.01% per year during 2008–2019. The bacteriologically confirmed TB and clinically confirmed TB patients dropped at a rate of 0.06% and 2.08% per year, respectively, during 2008–2019 (Figure 3B). The case fatality rate of TB dropped at a rate of 0.13% per year during 2008–2019. The case fatality rate of bacteriologically confirmed TB cases had a small increase trend during 2008–2019, increased at a rate of 0.11% per year while the clinically confirmed TB dropped at a rate of 1.95% per year (Figure 3C). However, all the trends have changed dramatically since the COVID-19 outbreak. The rate of TB treatment success showed a decline trend during 2019–2021, dropped at a rate of 11.80% per year. Meanwhile, the rate of poor outcomes showed a dramatic increase, increasing at

Table 3 Joinpoint Analysis in Notification Rates of Bacteriologically Confirmed TB in Shandong Province, 2005–2021

	Year	Notification rates of bacteriologically confirmed TB case[a]	Annual percent change (95% CI)	P value
Overall	2005–2010	38.7–27.3	−6.3(−8.7— −4)	< 0.001
	2010–2016	27.3–7.9	−20.2(−23.2— −17.2)	< 0.001
	2016–2021	7.9–8.5	3.4(−4.3—11.8)	0.354
Sex				
Male	2005–2010	53.1–38.7	−6.0(−8.2— −3.7)	< 0.001
	2010–2016	38.7–11.9	−19.3(−22.2— −16.4)	< 0.001
	2016–2021	11.9–12.1	1.7(−5.5—9.4)	0.621
Female	2005–2010	23.9–15.5	−7.1(−10— −4.2)	< 0.001
	2010–2016	15.5–3.8	−22.7(−26.4— −18.7)	< 0.001
	2016–2021	3.8–4.7	8.5(−2—20)	0.103
Age				
0–14	2005–2014	1.5–0.04	−29.5(−37.3— −20.7)	< 0.001
	2014–2021	0.04–0.3	37.0(0.5—86.7)	0.047
15–29	2005–2010	38.2–26.8	−6.8(−9.4— −4.1)	< 0.001
	2010–2017	26.8–4.8	−22.5(−25.3— −19.7)	< 0.001
	2017–2021	4.8–6.4	14.7(−6.9—41.3)	0.171
30–44	2005–2010	27.0–18.7	−6.1(−9.2— −3)	0.002
	2010–2016	18.7–4.4	−23.1(−27— −19)	< 0.001
	2016–2021	4.4–6.8	12.5(1.7—24.3)	0.027
45–59	2005–2010	43.5–30.4	−6.2(−9.2— −3)	0.002
	2010–2016	30.4–8.3	−20.6(−24.5— −16.5)	< 0.001
	2016–2021	8.3–8.9	0.9(−9.4—12.3)	0.86
≥60	2005–2010	91.6–66.5	−5.8(−8.5— −3.1)	0.001
	2010–2015	66.5–25.5	−18.4(−22.9— −13.7)	< 0.001
	2015–2021	25.5–22.3	−2.6(−8.5—3.6)	0.353
Treatment history				
New case	2005–2010	32.9–23.0	−6.8(−8.9— −4.6)	< 0.001
	2010–2016	23.0–6.8	−19.8(−22.6— −16.9)	< 0.001
	2016–2021	6.8–8.1	5.8(−1.3—13.4)	0.101
Relapse case	2005–2010	5.7–4.3	−4.2(−7.7— −0.5)	0.029
	2010–2021	4.3–0.4	−22.0(−24.5— −19.4)	< 0.001
Floating population				
No	2005–2010	38.4–25.4	−7.3(−10.2— −4.3)	< 0.001
	2010–2018	25.4–3.7	−20.8(−23.4— −18.2)	< 0.001
	2018–2021	3.7–6.5	15.6(−21.2—69.6)	0.414
Yes	2005–2009	0.21–1.7	89.9(28.8—180)	0.005
	2009–2013	1.7–0.4	−22.4(−45.4—10.4)	0.138
	2013–2021	0.4–1.9	25.2(14—37.5)	< 0.001
Residence				
Rural	2005–2010	33.5–23.0	−6.6(−9.5— −3.6)	0.001
	2010–2015	23.0–7.0	−21.1(−26— −15.8)	< 0.001
	2015–2021	7.0–3.8	−11.0(−18.7— −2.6)	0.017
Urban	2005–2010	5.2–4.3	−3.9(−8.2—0.5)	0.076
	2010–2016	4.3–1.4	−18.9(−23.8— −13.7)	< 0.001
	2016–2021	1.4–4.6	34.1(22.3—47)	< 0.001

Notes: [a] The notification rates of bacteriologically confirmed TB cases at the first and the last year of the segment.

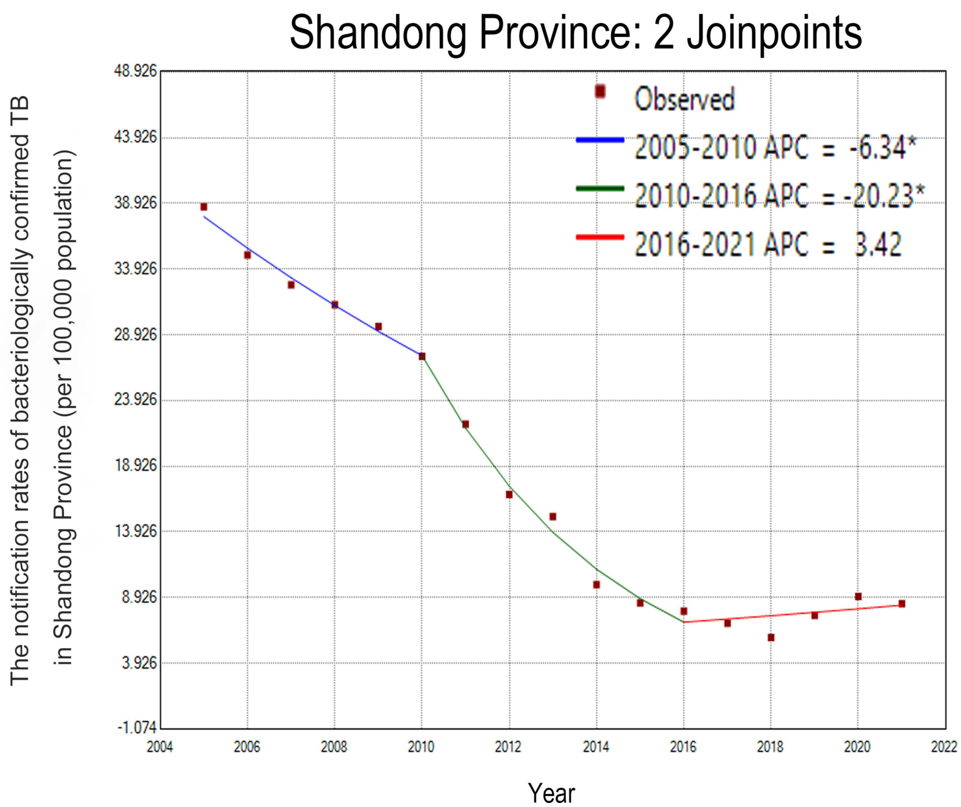

Figure 2 Change in notification rates of bacteriologically confirmed TB estimated by joinpoint model (solid line) in Shandong Province, 2005–2021. * $p<0.05$.

a rate of 805.63% per year. In particular, the rate of poor outcomes increased most significantly in clinically confirmed patients, increasing at a rate of 1425.51% per year. The case fatality rate of TB also showed a significant upward trend, increasing at a rate of 145.67% per year during 2019–2021. The case fatality rate of TB in bacteriologically confirmed cases and clinically confirmed cases increased at a rate of 42.60% and 144.08% per year, respectively (Table 4). In addition, we observed that compared with clinically confirmed TB, bacteriologically confirmed TB has shown higher rate of poor outcomes since 2008 and higher case fatality rate since 2005 (Figure 3B and C).

Discussion

This study calculated the trends of TB notification rates and the year-to-year changes of treatment outcomes in Shandong Province during 2005–2021. The primary conclusions of this study are as follows: (1) since 2008, the notification rates of registered TB in Shandong Province had shown a downward trend; (2) the notification rates of bacteriologically confirmed TB decreased significantly from 2005 to 2016, and then it held steady; (3) there has been no significant improvement in the treatment of TB during 2008–2019; however, the COVID-19 outbreak has made the treatment of TB even worse.

The notification rates of registered TB in different countries show different time trends. In India, the notification rates of registered TB decreased significantly in both men and women during 1990–2019, and the decline was greater in women.[15] In Singapore, the notification rates of registered TB declined from 58 per 100,000 in 1998 to an historic low of 35 per 100,000 in 2007, and then began to rise around 39 per 100,000 population since 2008.[17] As reported, notification rates of registered TB in China peaked in 2005 and has been declining at an average rate of 2.8% per year since then.[23] According to our research, the notification rates of registered TB in Shandong Province followed a same pattern, after a brief increase during 2005–2008, it has declined since 2008. Several government-implemented strategies in TB control contributed to the consistent drop in TB notification rates. The first was that the government expanded the DOTS programme nationwide. With funding from a World Bank loan, China adopted the DOTS in 13 provinces (including

Table 4 The Year-to-Year Changes of TB Cases in Shandong Province,2005–2021

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Changes 2005–2008(%)	Changes 2008–2019(%)	Changes 2019–2021(%)
Treatment success per100	90.66	90.50	87.41	95.91	96.41	96.34	96.74	97.16	97.13	96.46	97.18	96.14	95.79	96.32	97.06	92.94	91.15	0.74	0.01	−11.80
Bacteriologically confirmed cases	91.01	91.50	89.49	96.02	96.20	95.96	96.37	96.37	96.29	95.65	96.09	94.33	93.43	93.38	95.54	89.98	90.11	0.71	−1.94	−11.04
Clinically confirmed cases	89.21	87.05	82.81	95.72	96.75	96.93	97.16	97.69	97.63	96.76	97.53	96.73	96.50	97.31	98.05	96.31	92.40	0.87	0.08	−11.20
Poor outcomes[a] Per 100	9.34	9.50	12.59	4.09	3.59	3.66	3.26	2.84	2.87	3.54	2.82	3.86	4.21	3.68	2.94	7.06	8.85	−2.74	−2.01	805.63
Bacteriologically confirmed cases	8.99	8.50	10.51	3.98	3.80	4.04	3.63	3.63	3.71	4.35	3.91	5.67	6.57	6.62	4.46	10.02	9.89	−2.71	−0.06	391.84
Clinically confirmed cases	10.79	12.95	17.19	4.28	3.25	3.07	2.84	2.31	2.37	3.24	2.47	3.27	3.50	2.69	1.95	3.69	7.60	−2.87	−2.08	1425.51
TB case fatality rate per1000	2.89	2.96	3.33	3.31	3.46	3.26	3.46	2.76	2.62	1.88	1.36	3.58	2.27	1.72	3.53	6.41	5.53	−0.25	−0.13	145.67
Bacteriologically confirmed cases	3.22	2.99	4.12	4.37	4.03	4.49	4.67	4.37	3.47	4.35	2.64	7.90	6.67	2.28	7.43	7.25	8.87	0.05	0.11	42.60
Clinically confirmed cases	1.52	2.83	1.59	1.52	2.51	1.32	2.10	1.67	2.10	0.99	0.94	2.15	0.95	1.54	0.97	5.47	1.52	−1.17	−1.95	144.08

Notes:[a]Poor outcomes include treatment failed, died, lost to follow-up and not evaluated.

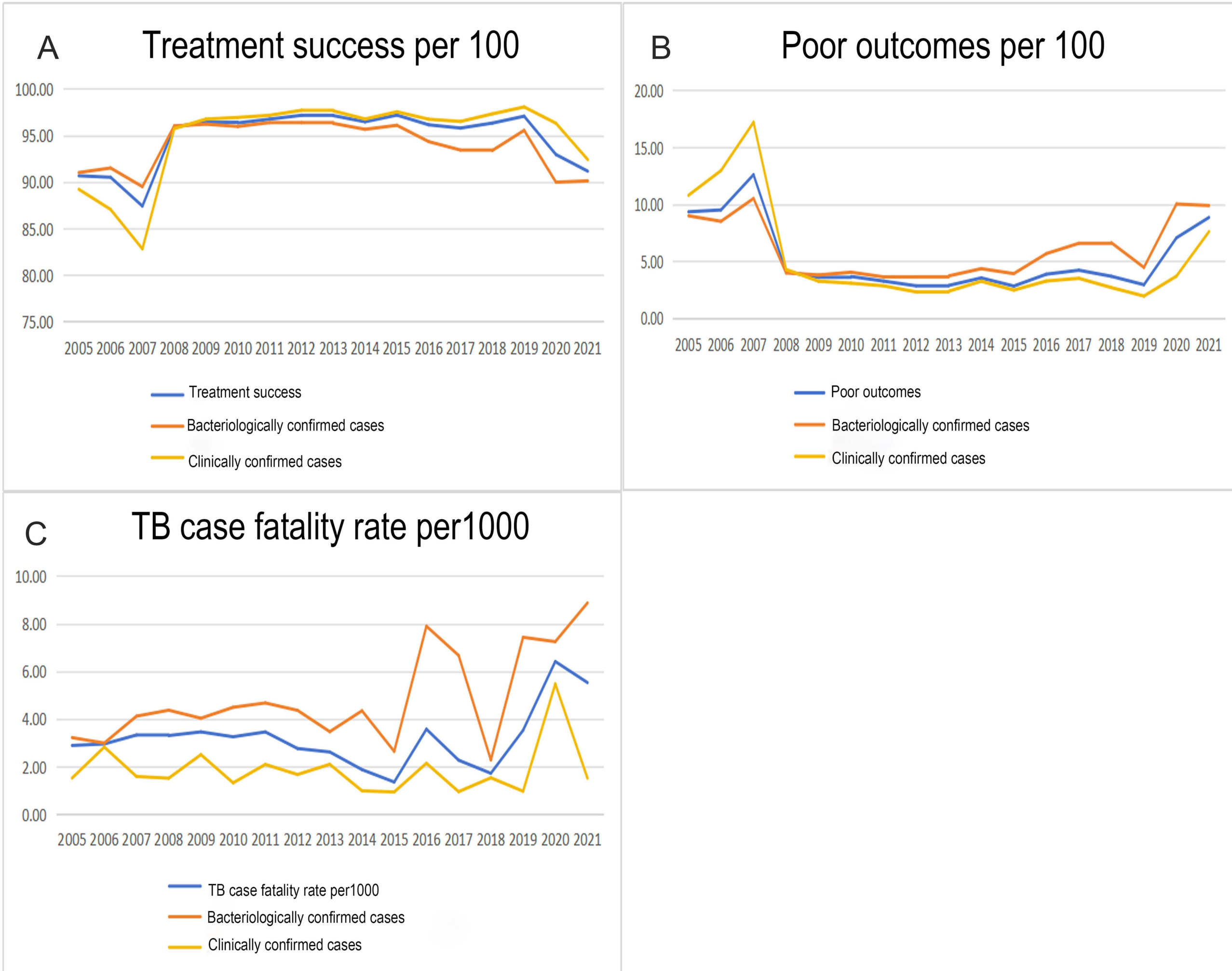

Figure 3 The changes of TB treatment outcomes in Shandong province,2005–2021.(**A**) The changes of TB treatment success rates; (**B**) The changes of TB treatment poor outcomes rates; (**C**) The changes of TB case fatality rates.

Shandong Province) during the 1990s, encompassing half of the nation's population.[6,24,25] TB case detection has significantly improved thanks to the DOTS approach. Then the State Council of China then released a new 10-year TB control plan in 2001, which extended the DOTS program across the entire nation by 2005.[7] In addition, the government paid more attention to public-health problems, especially after the outbreak of SARS in 2003. After the SARS pandemic, the State Council created a mechanism to supervise public-health emergencies directly.[24] What's more, the government has expanded its financial support for TB control and amended the law on the control of infectious diseases in 2004.[26] Moreover, in 2004, the largest internet-based communicable-disease reporting system in the world was put into place.[27] The internet-based reporting system has significantly reduced the time it takes to report infectious diseases and has made it possible for those working in TB control to quickly identify instances and guarantee that patients receive appropriate diagnosis and treatment.[1] The extensive use of the internet-based reporting system could be the reason for the increase in notified TB incidence in Shandong Province during 2005–2008. Since 2008 the notification rates of registered TB had significantly decreased in Shandong Province as a result of the consistent implementation of numerous policies, the continuous strengthening of public-health construction by the government and the rapid development of the economic level. Especially in 2008, the government launched a major special national science and technology project on the prevention and control of infectious diseases; since then, the project has improved and expanded the screening of infectious diseases, and has reduced even eliminated some cost in treatment.[1] All these strategies have played a crucial role in TB control.

In China, the notification rates of bacteriologically confirmed TB decreased by 48% between 1990 and 2010 (221 per 100,000 to 116 per 100,000).[7] Especially after the government expanded the DOTS strategy to the whole country, the notification rates of bacteriologically confirmed TB in all provinces decreased to varying degrees.[7] A previous study conducted in Shenzhen showed that the notification rates of bacteriologically confirmed TB showed a downward trend from 2011 to 2017, then increased significantly.[28] A previous study in Shandong Province also noted a decrease in the notification rates of bacteriologically confirmed (smear-positive) during 2005–2017 (33.23 per 100,000 to 6.41 per 100,000).[18] In our study, the notification rates of bacteriologically confirmed TB decreased significantly in Shandong Province from 2005 to 2016 (38.7 per 100,000 to 7.9 per 100,000). However, since 2016, the notification rates of bacteriologically confirmed TB tend to be stable and seems to be a growing trend (p=0.354), which could be associated with the extensive application of rapid molecular detection in clinical work. The application of molecular detection such as GeneXpert MTB/RIF substantially reduces the detection time of M. tb (less than 2 hours) and increases the sensitivity of the detection.[29,30] More bacteriologically confirmed TBs were being identified and treated after the extensive application of these novel diagnostic methods. Previous studies have indicated that bacteriologically confirmed TB had about four times the chance of spreading M. tb compared to those without confirmation.[31] Liu et al reported that the overall risk of death in bacteriologically confirmed patients (smear positive) was four times (Standard Mortality Ratio 4.1) that of the general population.[3] Furthermore, a bacteriologically confirmed TB case was more likely to develop multidrug-resistant tuberculosis (MDR-TB).[32] The recognition and treatment of bacteriological positive TB are vital for TB control.

The notification rates of registered TB and bacteriologically confirmed TB were higher in men, rural residents, and individuals ≥ 60 years in our study, which is similar to previous research.[33,34] Men may have an increased risk of active TB due to a sex hormone.[35–37] Previous research has shown that testosterone may decrease the generation of proinflammatory cytokines and interfere with macrophage activation, both of which may increase the risk of TB infection.[38] The differences might also have been influenced by the rates of drinking and smoking among the sexes. Smoking and alcohol consumption were found to be risk factors for active TB in earlier research.[39,40] The higher rates in rural areas may be closely related to economic level. It is possible that the worse living and economic circumstances in rural areas contributed to the rise in TB cases.[37] The causes and mechanisms behind the high notification rates of registered TB in the elderly are related to a number of risk factors, such as poor immunity with age increasing and combined with other diseases (such as COPD and diabetes).[34,41,42] According to the seventh national population census, the number of people aged ≥ 60 in Shandong Province is 21.221 million, accounting for 20.9%, and the degree of population aging is further deepened.[43] As a result, TB in the elderly has become an obstacle in the process of TB control.

In our study, changes in treatment outcomes shows a huge difference during 2008–2019 and 2019–2021. The changes in treatment outcomes from 2005 to 2008 may be related to the fact that the policies have just been implemented and have not yet been perfected. There was no significant improvement in the rate of poor outcomes during 2008–2019. This may be related to poor patient compliance. When compared to most bacterial infections, the current conventional 6-month treatment for drug-susceptible TB is lengthy.[44] One of the main obstacles to curing the disease is that many people find it difficult to finish their course of treatment.[45] A previous study detailed possible factors for poor patient compliance.[46] It pointed out that structural factors (poverty, gender, and discrimination), patient factors (motivation, knowledge, beliefs, attitudes and interpretations of illness and wellness), social environment and health care services may affect patient compliance.[46] Thus, more initiatives are required to enhance treatment compliance and reduce the worldwide burden of TB. We have also observed that after the COVID-19 outbreak in 2019, the rate of poor outcomes increased significantly. Similar studies also reported that patients who started treatment during the pandemic were 1.85 times (95% CI 1.46 to 2.36) more likely to have poor outcomes than those who started treatment before the pandemic.[47] A study conducted in Turkey found that the proportion of patients who failed treatment during the pandemic increased from 1.9% to 17% (p=0.018).[12] COVID-19 has put enormous pressure on healthcare systems and limited the provision of necessary medical services. The majority of attention from health system has shifted toward COVID-19.[8] And in response to the epidemic, many countries, including China, have imposed movement restrictions on large sections of the population.[48] To some extent, this policy has also limited access to basic health services and may have affected the diagnosis and treatment of other infectious diseases, such as TB. The rapid increase in the incidence of poor outcomes and case fatality rate after the COVID-19 outbreak is consistent with previous studies.[14,49,50] We also observed that the rate of poor outcomes and case fatality rate in clinically confirmed TB patients increased faster than those bacteriologically confirmed patients. This may be related to the fact that patients who are bacteriologically negative are more likely to be overlooked during the COVID-19 pandemic, and then delaying treatment. Bacteriologically confirmed patients had a higher rate of poor outcomes and case fatality rate, this consistent with previous researches.[2] COVID-19 has set TB control efforts back by about a decade,[49] and our research also confirms this. COVID-19 may be contained by vaccinations, but the impact will be felt for a long time. In the context of the continued existence of COVID-19, its impact on TB control still needs to be observed in the long term.

There are some limitations to the study. Firstly, we used the notification record data to do the analysis. The CDC provided all the information, and different judgments of disease information by treating doctors can lead to unavoidable bias. Secondly, the economic and geographical differences restricted the generalizability of the results because just one city on the eastern coast was studied. Therefore, there was bias to represent the situations of cities and provinces. Thirdly, drug-resistant TB and HIV/TB co-infection are also the big challenges of TB control. However, we were unable to examine the time trends of drug-resistant TB cases and the notification rates of HIV/TB co-infection cases in Shandong Province due to the lack of some data. Fourthly, we only collected data for two years after the COVID-19 outbreak. These data do not allow for a long-term assessment of the impact of COVID-19 on TB treatment and longer observations are needed to assess the impact of COVID-19 on TB control.

Conclusion

In conclusion, the notification rates of registered TB and bacteriologically confirmed TB declined during 2005–2021 in Shandong Province owing to unremitting TB control efforts. The rate of poor outcomes showed a steady trend during 2008–2019, then rise significantly after the COVID-19 outbreak. The COVID-19 undoubtedly has had a devastating impact on the prevention and control of TB. In the context of the long-term existence of COVID-19, further efforts should be made in TB diagnosis and treatment among high-risk population, especially with regard to males, rural residents and older adults to achieve the End TB Strategy by 2035.

Abbreviations

CDC, Center for Disease Control and Prevention; APC, annual percentage change; M. tb, Mycobacterium tuberculosis; DOTS, Directly Observed Therapy, Short Course; PTB, Pulmonary tuberculosis; 95% CI, 95% confidence interval.

Data Sharing Statement

The data used and analyzed during the current study is not publicly available. For any inquiries, please contact the corresponding author.

Ethics Approval and Consent to Participate

All patient identifiers were removed prior to data analysis and reporting, therefore informed permission was not necessary. The Ethics Committee of Shandong Provincial Hospital affiliated with Shandong First Medical University, China, granted a waiver of informed consent and granted ethical approval for the study. According to the Declaration of Helsinki, the study was carried out.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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