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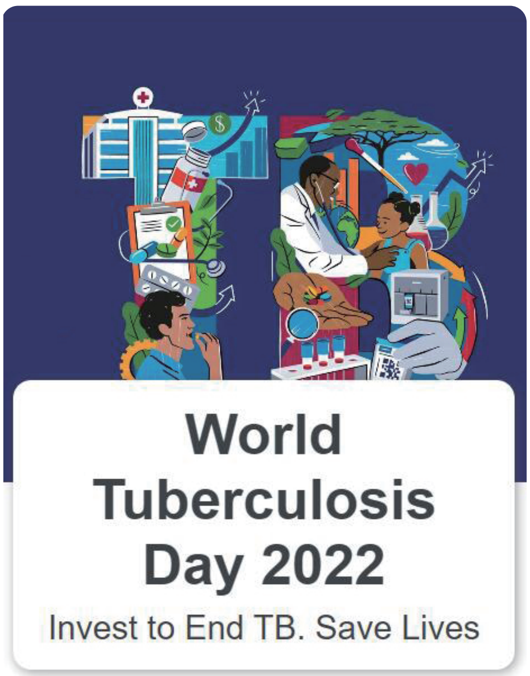

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Preplanned Studies

Acceptability of Tuberculosis Preventive Treatment Strategies Among Healthcare Workers Using an Online Survey — China, 2021

Lifeng Fa[1]; Caihong Xu[1]; Jun Cheng[1]; Hui Zhang[1,#]

Summary

What is already known about this topic?

In the absence of effective vaccines, tuberculosis preventive treatment (TPT) is essential for the rapid decrease in incidences of tuberculosis (TB), and healthcare workers' acceptability is vital to implementing TPT.

What is added by this report?

Overall, 86.5% of healthcare workers knew what TPT was. Most (56.3%) healthcare workers agreed to implement TPT among high-risk groups with latent tuberculosis infection. Drug resistance, adverse events, and unguaranteed efficacy were three main barriers for healthcare workers in accepting TPT.

What are the implications for public health practice?

To further promote and implement TPT in China, practical measures included policy support, high-quality training for healthcare workers, and enhanced public awareness of TB prevention and control.

It is estimated that about 1/4 of the world's population is latently infected with mycobacterium tuberculosis (MTB) (*1*). Previous studies showed that 5% to 10% of latent tuberculosis infection patients (LTBIs) might develop active tuberculosis (TB) if left untreated (*2*). Tuberculosis preventive treatment (TPT), with no effective vaccines, is essential for decreasing TB incidence. The World Health Organization (WHO) has made TPT an essential component of the "End TB Strategy" since 2010. TPT pilot studies among college students, close contacts of infectious patients, and people living with human immunodeficiency virus (PLHIV) in some provinces in China started in the 1990s. China is the second highest TB burden country, accounting for 8.5% of estimated incident cases globally (*3*). At present, there are no implementation requirements for high-risk groups in the National TB Program (NTP), except for student close contacts of pulmonary tuberculosis (PTB) patients.

A questionnaire was generated using an online survey tool Wenjuanxing (WJX, https://www.wjx.cn/, in Chinese). Considering TB burden status and economic levels, we selected Beijing, Tianjin, Shanghai, and five provinces in each of China's eastern, central, and western regions. The survey was conducted from November 18 to December 9 in 2020. Questionnaires were delivered to the heads of provincial-level CDCs, who then distributed the questionnaires to other leaders at the municipal and county levels, which were then distributed to WeChat groups to be filled out voluntarily by healthcare workers (HCWs). Questions included demographic characteristics, whether HCWs have heard of TPT, acceptability to implement TPT, the reasons for disagreeing with TPT, and preconditions that China should have to implement TPT. Data were collected through WJX, cleaned in Microsoft Office Excel (version 2016; Microsoft Corp, Washington, USA) and analyzed with SAS (version 9.4, SAS Institute, Inc. Cary, NC, USA). We presented categorized variables as frequencies and proportions. Logistic regression was used to assess associations between demographic characteristics and survey responses with a significance of α =0.05. Multivariable analysis included adjustment for age, gender, education level, institution, region, and years of experience as a TB HCW.

A total of 5,547 HCWs participated in the survey, with a mean age of (40.9±8.9) years. Among them, 2,057 (37.1%) were males, 1,965 (35.4%) were from central region, 2,788 (50.3%) had bachelor degrees and 3,382 (61.0%) had engaged in TB control for 10 years or fewer. Of all participants, 4,796 (86.5%) HCWs heard of TPT.

Fewer female HCWs had heard of TPT than male HCWs [adjusted odds ratio (OR)=0.735, 95% confidence interval (CI): 0.616–0.876, P<0.001]. A higher proportion of HCWs with postgraduate or higher education (adjusted OR=4.515, 95% CI: 2.134–9.550, P<0.001) had heard of TPT compared with those with secondary or lower education. Compared to the CDC, a lower proportion of HCWs in TB designated hospital (adjusted OR=0.621, 95% CI: 0.497–0.776, P<0.001) and primary health care institutions (adjusted OR=0.360, 95% CI: 0.283–0.457, P<0.001) had heard of TPT. Years of experience as a TB HCW was positively associated with having heard of TPT (Table 1).

Among HCWs who had heard of TPT, 1,421 (29.6%) agreed to implement TPT among all LTBIs, 2,698 (56.3%) agreed to implement TPT among high-risk populations with LTBI, 528 (11.2%) held neutral attitudes, and 139 (2.9%) did not agree. In CDC and TB designated hospitals, a high proportion of HCWs agreed to carry out TPT among high-risk populations with LTBI. In primary healthcare institutions, HCWs agreeing to implement TPT among all LTBIs were in roughly the same proportions as HCWs agreeing to implement TPT among high-risk populations with LTBI (Table 2).

Among the 139 HCWs who disagreed with TPT, the reasons why they disagreed with TPT were the

TABLE 1. Characteristics of HCWs who had heard of TPT in China, 2020.

Factor	HCWs who had heard of TPT (n, %)	HCWs who had not heard of TPT (n, %)	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Total	4,796/5,547 (86.5)	751/5,547 (13.5)				
Age, years						
≤30	719 (84.0)	137 (16.0)	1.000		1.000	
31–40	1,521 (86.3)	241 (13.7)	1.203 (0.958–1.510)	0.112	0.965 (0.762–1.222)	0.766
41–50	1,790 (87.2)	264 (12.8)	1.293 (1.033–1.616)	0.025	0.958 (0.749–1.225)	0.730
≥50	766 (87.5)	109 (12.5)	1.339 (1.021–1.757)	0.035	0.783 (0.569–1.078)	0.134
Gender						
Male	1,835 (89.2)	222 (10.8)	1.000		1.000	
Female	2,961 (84.8)	529 (15.2)	0.677 (0.573–0.801)	<0.001	0.735 (0.616–0.876)	<0.001
Education Level						
Senior high school degree or below	585 (81.9)	129 (18.1)	1.000		1.000	
Junior college	1,488 (84.0)	284 (16.0)	1.155 (0.919–1.453)	0.217	1.013 (0.794–1.291)	0.919
Bachelor degrees	2,458 (88.2)	330 (11.8)	1.642 (1.315–2.052)	<0.001	1.209 (0.940–1.553)	0.139
Postgraduate and above	265 (97.1)	8 (2.9)	7.303 (3.524–15.135)	<0.001	4.515 (2.134–9.550)	<0.001
Institution						
CDC	1,454 (92.1)	124 (7.9)	1.000		1.000	
Designated TB hospital	2,292 (87.6)	324 (12.4)	0.603 (0.486–0.750)	<0.001	0.621 (0.497–0.776)	<0.001
Primary health care institutions	1,050 (77.6)	303 (22.4)	0.296 (0.236–0.370)	<0.001	0.360 (0.283–0.457)	<0.001
Region						
Beijing, Tianjin, Shanghai	321 (88.9)	40 (11.1)	1.000		1.000	
East	1,731 (88.7)	220 (11.3)	0.980 (0.686–1.402)	0.913	1.215 (0.839–1.760)	0.302
Middle	1,626 (82.8)	339 (17.2)	0.598 (0.422–0.847)	0.004	0.713 (0.497–1.023)	0.067
West	1,118 (88.0)	152 (12.0)	0.917 (0.633–1.327)	0.644	0.961 (0.656–1.409)	0.840
Years of experience as a TB HCW, year						
≤10	2,830 (83.7)	552 (16.3)	1.000		1.000	
11–20	1,164 (90.6)	120 (9.4)	1.892 (1.535–2.332)	<0.001	1.596 (1.274–2.001)	<0.001
21–30	674 (90.7)	69 (9.3)	1.905 (1.463–2.481)	<0.001	1.823 (1.352–2.458)	<0.001
≥31	128 (92.8)	10 (7.2)	2.497 (1.303–4.782)	0.006	2.555 (1.271–5.137)	<0.001

Abbreviations: HCWs=healthcare workers; TPT=tuberculosis preventive treatment; OR=odds ratio; CI=confidence interval; TB=tuberculosis.

TABLE 2. Acceptability of HCWs on TPT in different institutions in China, 2020.

Organization	Agree TPT for all people with LTBI, n (%)	Agree TPT for key groups with LTBI, n (%)	Neutrality, n (%)	Disagree, n (%)	Total, n
CDC	309 (21.3)	915 (62.9)	171 (11.8)	59 (4.1)	1,454
Designated TB hospital	646 (28.2)	1,313 (57.3)	275 (12.0)	58 (2.5)	2,292
Primary health care institutions	466 (44.4)	470 (44.8)	92 (8.8)	22 (2.1)	1,050
Total	1,421 (29.6)	2,698 (56.3)	538 (11.2)	139 (2.9)	4,796

Abbreviations: HCWs=healthcare workers; TPT=tuberculosis preventive treatment; LTBI=latent tuberculosis infection; TB=tuberculosis.

following, in order: "Worrying about acquired drug resistance" (72.7%, 101/139); "Worrying about adverse events" (70.5%, 98/139); "Unguaranteed efficacy" (69.8%, 97/139); "Lacking financial support" (35.3%, 49/139); "Lacking sufficient staff" (34.5%, 48/139); "Troublesome administration of medication" (28.1%, 39/139); and "No policy support" (28.1%, 39/139).

This showed how HCWs think that "high acceptability of TPT of the TPT target population and their families," "HCWs with enough professional knowledge of TPT," and "policy support" were three primary preconditions for China to implement TPT. The proportions of HCWs in CDC and TB designated hospitals were roughly the same. In multivariable logistic regression, statistically significant differences in the perceptions were found in "HCWs with professional knowledge of TPT" and "adequate staff" among HCWs in different institutions (Table 3).

DISCUSSION

The results showed that 86.5% of HCWs had heard of TPT. Although TPT is not included in the NTP, it is regarded as an important technical measure in the "*Chinese Technical Specification for Tuberculosis Prevention and Control"* issued in 2020. This shows a certain basis of TPT in China, and thus a high percentage of HCWs have heard of TPT. However, primary HCWs (PHCWs) were the least familiar with TPT. HCWs with more years of experience in TB control and higher education have a stronger ability to obtain information actively, so they are more likely to have heard of TPT.

TPT should be selectively implemented on populations with the highest risk of progression to active TB, who would benefit most from it. Most HCWs (56.3%) agreed to carry out TPT among high-risk populations with LTBI, as the risk of developing active TB is particularly elevated among children under the age of 5 years, human immunodeficiency virus /acquired immunodeficiency syndrome, and people with compromised immunity (*4*–*5*). It was estimated that about 360 million people are latently infected with MTB in China, which makes TPT challenging because of difficult medication management, enormous costs, and the risk of severe adverse events. However, nearly half (44.4%) of the PHCWs lack awareness of recommendations on TPT proposed by WHO. To change this situation, we should strengthen the professional training of PHCWs and HCWs on TPT understanding.

In this study, a minority of HCWs were against TPT due to their perception of drug resistance, adverse events, and unguaranteed efficacy, resulting from insufficient TPT knowledge. Currently, there is no evidence of drug resistance caused by TPT. The incidence of adverse events is low, and TPT efficacy is high (*6*). TPT has not been effectively used in the past, and standardized treatment of LTBI will help to achieve NTP. Therefore, there is a need to provide updated evidence related to TPT to improve understanding of the benefits and risks of TPT among HCWs.

This study was subject to some limitations. This was an online survey using a convenience sampling method. Although this study had extensive geographic coverage across China and a large sample size, participants' representativeness might be limited. Futhermore, the acceptability of TPT was self-reported, and there were no repeated verification questions or detailed resources included in the questionnaire.

In order to further promote the implementation of TPT in China, the government and other relevant departments need to provide adequate personnel, funding, and policy support for TPT. Further studies are necessary to model the impact of TPT on morbidity, evaluate the economic benefits of TPT reducing TB burden, and assess patients' perceptions of TPT and efficacy in order to address the concerns of the government, TB HCWs, and patients and promote the implementation of TPT in China (*7*).

TABLE 3. The opinions on preconditions for implementing TPT among HCWs in China, 2020.

Question	Yes, n (%)	No, n (%)	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Q1: Do you think the TPT target population and their families should have high acceptability toward TPT?						
All	4,123/4,796 (86.0)	673/4,796 (14.0)				
CDC	1,232 (84.7)	222 (15.3)	1.000		1.000	
TB designated hospital	1,990 (86.8)	302 (13.2)	1.187 (0.985–1.432)	0.072	1.140 (0.941–1.382)	0.182
Primary healthcare institutions	901 (85.8)	149 (14.2)	1.090 (0.870–1.364)	0.454	1.263 (0.990–1.611)	0.060
Q2: Do you think HCWs should have enough professional knowledge of TPT?						
All	3,850/4,796 (80.7)	946/4,796 (19.3)				
CDC	1.089 (74.9)	365 (25.1)	1.000		1.000	
TB designated hospital	1,904 (83.1)	388 (16.9)	1.645 (1.400–1.933)	<0.001	1.585 (1.343–1.870)	<0.001
Primary healthcare institutions	857 (81.6)	193 (18.4)	1.489 (1.224–1.811)	<0.001	1.737 (1.404–2.150)	<0.001
Q3: Do you think implementing TPT should have adequate staff?						
All	2,958/4,796 (62.0)	1,838/4,796 (38.0)				
CDC	844 (58.1)	610 (41.9)	1.000		1.000	
TB designated hospital	1,429 (62.4)	863 (37.6)	1.197 (1.047–1.369)	0.009	1.181 (1.029–1.355)	0.018
Primary healthcare institutions	685 (65.2)	365 (34.8)	1.356 (1.151–1.599)	<0.001	1.313 (1.100–1.568)	0.003
Q4: Do you think implementing TPT needs financial support?						
All	3,284/4,796 (68.5)	1,512/4,796 (31.5)				
CDC	1.002 (68.9)	452 (31.1)	1.000		1.000	
TB designated hospital	1,553 (67.8)	739 (32.2)	0.948 (0.823–1.092)	0.459	0.955 (0.827–1.104)	0.533
Primary healthcare institutions	729 (69.4)	321 (30.6)	1.024 (0.863–1.217)	0.783	1.083 (0.900–1.304)	0.399
Q5: Do you think implementing TPT needs professional guidance from relevant experts?						
All	3,222/4,796 (67.2)	1,573/4,796 (32.8)				
CDC	981 (67.5)	473 (32.5)	1.000		1.000	
TB designated hospital	1,539 (67.2)	753 (32.8)	0.985 (0.857–1.134)	0.838	0.984 (0.852–1.136)	0.823
Primary healthcare institutions	702 (66.9)	348(33.1)	0.973 (0.821–1.152)	0.748	0.999 (0.832–1.200)	0.994
Q6: Do you think implementing TPT needs policy support?						
All	3,315/4,796 (69.1)	1,481/4,796 (30.9)				
CDC	1,010 (69.5)	444 (30.5)	1.000		1.000	
TB designated hospital	1,620 (70.7)	672 (29.3)	1.060 (0.918–1.223)	0.427	1.075 (0.928–1.245)	0.334
Primary healthcare institutions	685 (65.2)	365 (34.8)	0.825 (0.697–0.977)	0.026	0.883 (0.735–1.061)	0.185

Abbreviations: TPT=tuberculosis preventive treatment; HCWs=healthcare workers; OR=odds ratio; CI=confidence interval; TB=tuberculosis.

Acknowledgments: The staff in the provincial-level CDCs, local CDCs, TB designated hospitals, and primary healthcare institutions.

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Corresponding author: Hui Zhang, zhanghui@chinacdc.cn.

[1] National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

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Preplanned Studies

The Impact of COVID-19 Epidemic on Tuberculosis Reports Among Students — Guizhou Province, China, 2020

Yuying He[1]; Tao Li[2]; Lijie Zhang[3]; Renzhong Li[2]; Zaiping Chen[1]; Yunzhou Ruan[2]; Wei Su[2]; Jinlan Li[1,#]

Summary

What is already known about this topic?

In 2020, the implementation of non-medical interventions during the coronavirus disease 2019 (COVID-19) epidemic has created a negative impact on tuberculosis (TB) control. It is unclear if the prevalence of TB among students in Guizhou Province was also affected.

What is added by this report?

Among TB cases, the proportion of student TB patients was 19.91% in the back-to-school period in 2020, which was higher than the 13.37% registered in 2017–2019, but this decreased in the COVID-19 pandemic period. The time interval between symptom onset and care-seeking of the student TB patients was the shortest in the back-to-school and physical check-up periods.

What are the implications for public health practice?

TB active screening was effective for timely detection and diagnosis of TB among students, which could prevent TB outbreaks in schools.

During the COVID-19 epidemic in 2020, district blockages, community and traffic restrictions, and public recreation and school closure (*1–2*) all caused delays in tuberculosis (TB) diagnoses, reducing the registered number of TB cases and possibly resulting in additional deaths. This was due to a decrease in detection of TB patients (*3–5*), which might have the same effect on TB among students. Students are one of the key groups for TB prevention and control in China (*6*). Due to COVID-19, students stayed at home for nearly four months for winter vacation. The Guizhou Provincial Health Commission required students with a cough and expectoration to go to a TB-designated hospital for chest radiography to rule out TB before returning to school. The data was collected from the TB Information Management System (TBIMS) of China. The 2020 data used for analysis was collected between January 24 and June 24, as this was the time when the COVID-19 response was implemented in Guizhou. We divided the response into three periods based on three key time points. The 2017–2019 data from the same time frame as that of 2020 were used for comparison. They were also divided into three corresponding periods. Analysis showed that the registered student TB rates in 2020 decreased in the first and second periods, but increased in the third period compared to 2017–2019, whereas the total registered TB cases in Guizhou decreased. In 2020, the time interval between symptom onset and care-seeking of the TB among students in third period was shorter than the interval in the first period and the second period. This study showed that carrying out active screening for students is an important strategy for early detection of TB patients, which could offset the negative impacts of COVID-19 on TB detection and prevent TB outbreaks in schools.

Data in this analysis was from the TBIMS of China, from which data of student TB patients registered in Guizhou Province was derived from 2017 to 2020. We divided the COVID-19 response in Guizhou into three periods based on three key time points: the first period was from January 24 to February 27, 2020, when Guizhou started the highest level COVID-19 response, namely the COVID-19 pandemic period; the second period was from February 28 to May 1, 2020, when people resumed work, namely the work resumption period; and the third period was from May 2 to June 24, 2020, when students went back to school and had their physical check-up for college entrance examination, namely the back-to-school, as well as intensive physical check-up period. We divided 2017–2019 into the same periods, the three years prior to the COVID-19 epidemic. In 2017–2019, the return to school and college entrance examination physical check-up took place in the second period (March to May) rather than in the third period. The number of registered TB patients in the whole population and among students was counted in weeks, and SPSS (version 26.0, IBM Corp., Armonk, NY) was used for statistical analysis. Countable variables were presented by number of cases and percentage. Chi-squared tests were used for categorical data, and Kruskal-Wallis tests were used for continual data. $P<0.05$ was considered statistically significant.

In 2020, the numbers of registered TB patients in Guizhou Province in the three periods were 2,017 cases, 6,370 cases, and 5,917 cases, respectively, a decrease of 31.67%, 12.58%, and 4.39% compared with the mean registered cases in the same periods in 2017–2019.

In 2020, the number of registered TB patients among students in the three periods was 216 cases, 813 cases, and 1,178 cases, respectively (Figure 1). While compared with the mean cases of the previous 3 years, it was found that in 2020 the number decreased by 36.22% and 16.50% in the first and second periods, respectively, but increased by 100.34% in the third period. In 2020 and the previous 3 years, the student TB cases who were found during the period of back-to-school and intensive physical check-up for entrance examination of college accounted for 19.91% (1,178/5,917) and 13.37% (974/7,287) of the total registered TB cases respectively, and the difference was statistically significant ($P<0.05$)(Figure 2).

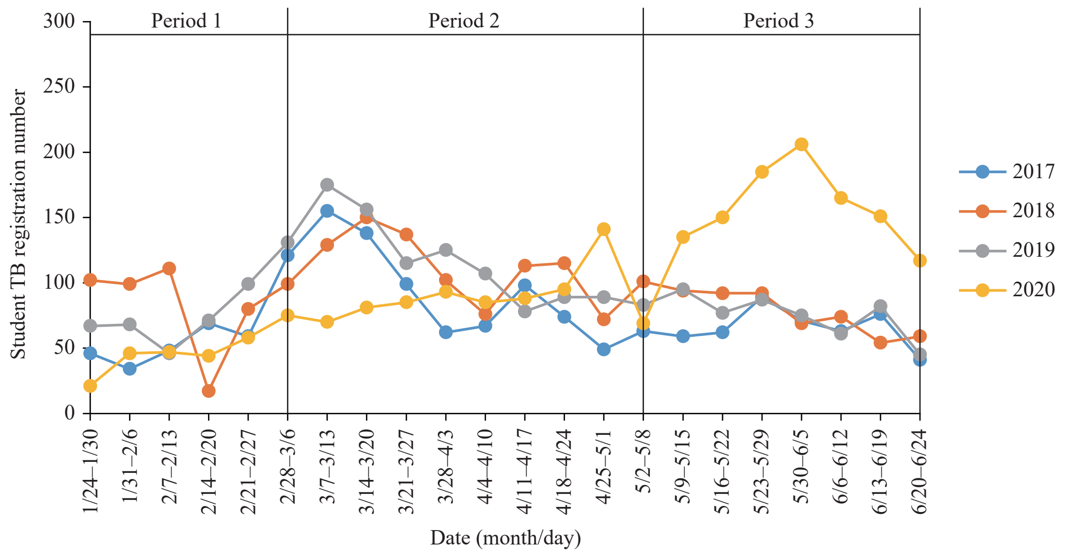

FIGURE 1. The registration number of tuberculosis (TB) among students in 3 periods, Guizhou Province, 2017–2020.

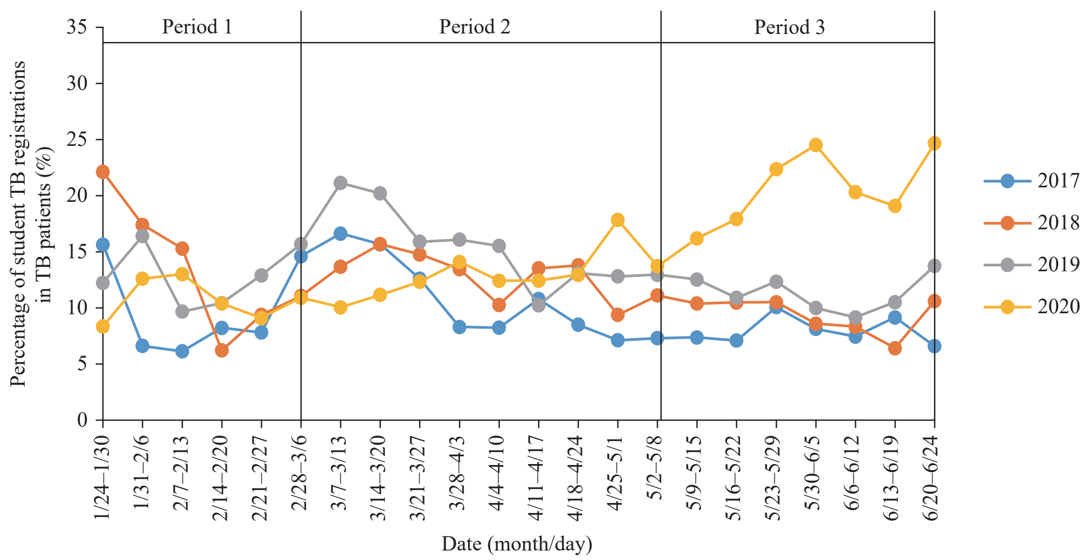

FIGURE 2. The proportion of student patients among total tuberculosis (TB) cases in 3 periods, Guizhou Province, 2017–2020.

The median of the interquartile range (IQR) of time interval between symptom onset and care-seeking of the student TB patients in 2020 was 18 (7–63) days in the first period, 19 (7–45) days in the second period, and 13 (3–32) days in the third period. The difference between the first two and the third periods was statistically significant (P<0.05). Similarly, in 2017–2019, the median of the IQR of time interval between symptom onset and care-seeking in the second period (back-to-school and intensive physical check-up) was shorter than the other two periods. The difference was also statistically significant (P<0.05) (Figure 3).

DISCUSSION

In the first period of the COVID-19 epidemic, the registration number of TB patients (including student patients) in Guizhou dropped by a third compared with the mean number of the previous 3 years in the same period, which is consistent with reports from China and other countries (*1*,*3*–*4*). The reported TB incidence among students in China peaked from March to April each year, which could be explained by the intensive physical check-up for the entrance examination of college (*6*). This is inconsistent with the peak of student TB registration in Guizhou Province in 2017–2019. Due to the impact of the COVID-19 pandemic, the intensive physical check-up in the second period (February 28 to May 1) in 2017–2019 was postponed to the third period (from May 2 to June 24) in 2020, leading to a shift of the peak of student TB registration. Since Guizhou is a province with a high burden of TB, long exposure in the family is also one of the risk factors that increases TB (*7*). Therefore, it is required that students in Guizhou with symptoms of coughing and expectoration are evaluated for TB with a chest radiograph at a designated TB hospital before resuming school. The implementation of the new screening measure in 2020 detected more TB patients, resulting in a significantly higher registration number of student TB in the back-to-school and physical check-up for entrance examination period (May 2 to June 24) than in the first and second period. The pattern was also observed in the back-to-school and intensive physical check-up period (February 28 to May 1) in 2017–2019.

In both 2020 and 2017–2019, the time interval between the onset of symptoms and seeking medical care of student TB patients was similar. The interval in the intensive physical check-up period was shorter than that in other periods, which indicated that active screening plays a positive role in early detection of TB patients. Since most student TB patients were detected through physical check-up and most have no symptoms before diagnosis (*8*), it can be assumed that the students who were infected with *Mycobacterium tuberculosis* before and during the COVID-19 epidemic but had no symptoms would not have been found out if they had not got the physical check-up. It was also assumed that if there were no implementations of the new policy of active screening,

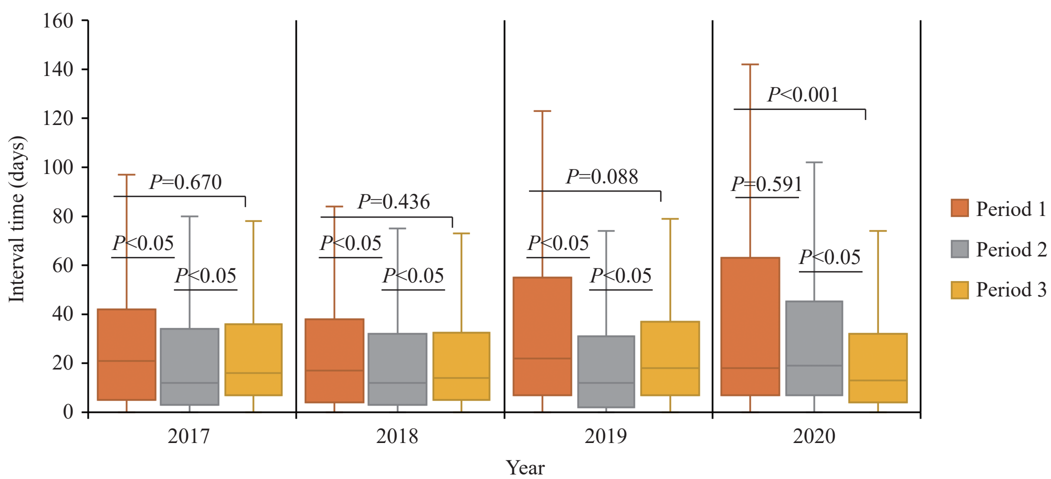

FIGURE 3. The comparison interval time between first symptom onset and first seeking medical care/physical check-up of student tuberculosis patients in the 3 periods in 2017–2020.
Note: Boxplot was used for describing the distribution of interval along y axis, the line inside the box was median. P value: Kruskal-Wallis Test, P value <0.05 was considered significant.

those who had symptoms but did not go to the doctor would not have been diagnosed in a timely manner. Therefore, whether the COVID-19 epidemic affects the time interval for student TB is still uncertain.

A limitation of this study was that although more students with tuberculosis were found through active screening, we did not have information on suspected TB symptoms and chest radiograph results of these cases. We were unable to do further analysis on the effectiveness of the active screening strategy on finding asymptomatic patients or patients with varying degrees of abnormal pulmonary changes indicated by chest radiography.

In conclusion, this study suggests that after students leave campus and stay at home for a long time, using chest radiography to screen those with suspicious symptoms before resuming school can be an effective measure for the early detection, early diagnosis, and early treatment of student TB patients. It can also be an important intervention for reducing TB outbreak in schools.

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Corresponding author: Jinlan Li, 740820442@qq.com.

[1] Institute for Tuberculosis Control, Guizhou Center for Disease Control and Prevention, Guiyang, Guizhou, China; [2] National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [3] Chinese Field Epidemiology Training Program, Chinese Center for Disease Control and Prevention, Beijing, China.

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Preplanned Studies

Application of Disability-Adjusted Life Years to Evaluate the Burden and Trend of Tuberculosis — China, 1990–2019

Zhe Dong[1]; Qiqi Wang[1]; Shicheng Yu[1]; Jianjun Liu[1]; Hui Zhang[1]; Fei Huang[1]; Hongyan Yao[1,#]

Summary

What is already known about this topic?

China is a country with a high burden of tuberculosis (TB). However, the evaluation of TB burden is usually based on traditional epidemiological indicators, and disability-adjusted life year (DALY) is rarely applied.

What is added by this report?

In China, the number of DALYs caused by TB in 2019 was estimated to be 1.36 million, and the age-standardized rate (ASR) was 86.46/100,000. The DALYs of TB decreased significantly from 1990 to 2019, with the largest decline from 2001 to 2010. The burden is higher among men than women, and the highest among the elderly.

What are the implications for public health practice?

Application of DALYs can reflect the damage in health to China's residents caused by tuberculosis. In the future, we should strengthen research, monitor years lived with disability (YLDs), and reduce the burden of the elderly and men. Cost-effective analysis based on DALYs should be conducted to provide a scientific basis for decision-making.

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (Mtb) infection. The treatment cycle is long and has caused heavy burden to the state, society, and individuals (*1*). Traditional epidemiological indicators, such as incidence and mortality rate, are often used to evaluate the burden of TB in China (*2*). Disability-adjusted life year (DALY) is a representative indicator widely used in the study of disease burden, summing year of life lost (YLL) and year lived with disability (YLD) (DALY= YLL+YLD). It comprehensively measures the loss of health caused by disease onset, premature death, and disability.

In China, DALY is seldom used in the field of tuberculosis (*2*). The 2019 global disease burden study (GBD 2019) estimates the burden of TB in China using population registration, census data, China National Disease Surveillance Points (DSP), mortality registration and reporting system, China National Maternal and Child Health Surveillance System (MCHS), WHO Mortality Database, WHO's Global TB Database, and other data sources (*3*–*6*). China has issued a number of national control plans since 1978 and carried out TB prevention and control according to those plans. Based on the GBD 2019, this study analyzed the trend of TB burden in China at different periods from 1990 to 2019.

This study obtained the DALY, YLS, and YLD caused by TB in China from 1990 to 2019, grouped by age and gender, using corresponding ratios and 95% uncertainty intervals (UIs) for data analysis. The 2010 national census was used as the standard population to calculate the age-standardized rate (ASR). And the estimated annual percentage change (EAPC) used to measure the trend of ASRs in a specific time interval. According to the national TB prevention and control plans published since 1990, 4 intervals (1990 to 2000, 2001 to 2010, 2011 to 2015, and 2016 to 2019) were used to reflect trends.

The time (year) was the independent variable x and the natural logarithm of the rate as the dependent variable for regression line fitting, $\gamma = \alpha + \beta x + \epsilon$, where γ=ln(ASR). α, β, and ϵ represented the intercept, slope, and residual of the line, respectively. EAPC [95% confidence interval (CI)] was calculated by substituting the formula $100 \times (\exp(\beta) - 1)$. If both EAPC and the upper limit of its 95% CI were greater than 0, it meant that ASRs were showing an upward trend; conversely, when both were less than 0, ASRs were showing a downward trend; other conditions indicate that ASRs showed a stable trend over time (*5*–*6*). The percentage change of the quantity was calculated by dividing the difference between the two time points by the value at the first point. Excel (version 2013, Microsoft, USA) and SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) software were used for data analysis and graphing (P<0.05).

According to Figure 1 and Table 1, YLLs, YLDs, and DALYs showed a significant downward trend from

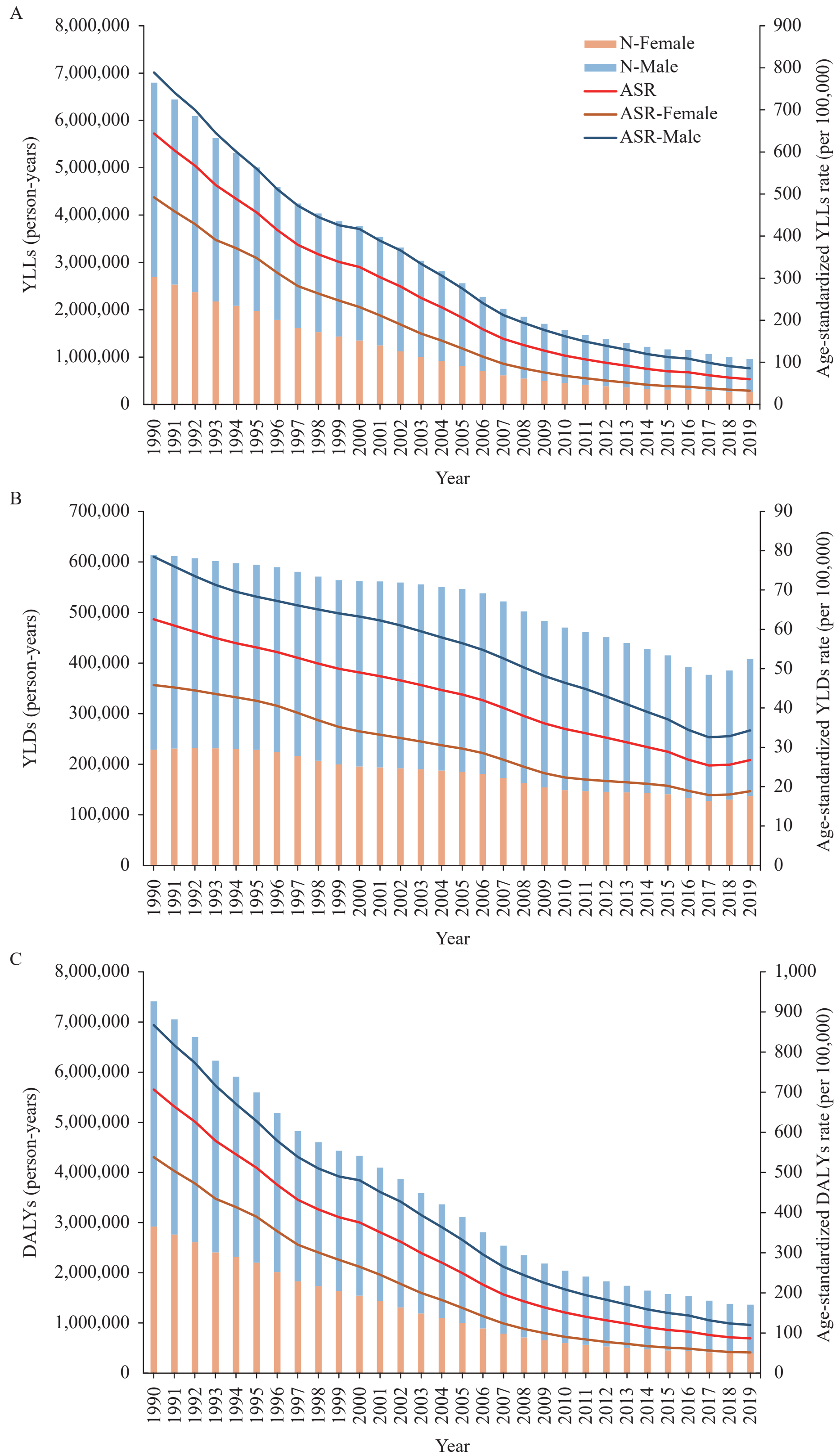

FIGURE 1. The number and age-standardized rates of disease burden caused by TB in China, 1990–2019. (A) TB related YLLs; (B) TB related YLDs; (C) TB related DALYs.

Abbreviations: TB=Tuberculosis; YLLs=years of life lost; YLDs=years lived with disability; DALYs=disability-adjusted life years; N=number; ASR=age-standardized rate.

TABLE 1. DALYs, YLLs, and YLDs of TB and their piecewise trend — China, 1990–2019.

Indictor/ Gender	1990		2019		1990–2000		2001–2010		2011–2015		2016–2019		1990–2019	
	N (95% UI)	ASR (1/100,000)	N (95% UI)	ASR (1/100,000)	P′	EAPC (95% CI)	P′	EAPC (95% CI)	P′	EAPC (95% CI)	P′	EAPC (95% CI)	P′	EAPC (95% CI)
YLLs														
Male	411 (351, 465)	788.76 (646.53, 935.15)	70 (56, 86)	85.66 (67.73, 106.14)	−41.07	−6.63 (−7.09, −6.16)	−51.12	−9.76 (−10.30, −9.21)	−19.05	−6.92 (−7.37, −6.46)	−16.49	−7.76 (−9.84, −5.62)	−82.95	−7.65 (−7.88, −7.43)
Female	269 (223, 309)	492.27 (389.69, 594.52)	26 (20, 34)	32.51 (25.00, 43.85)	−49.89	−7.47 (−7.80, −7.14)	−63.86	−12.22 (−12.72, −11.72)	−24.88	−8.7 (−9.40, −7.99)	−17.36	−8.25 (−10.07, −6.39)	−90.48	−9.57 (−9.88, −9.26)
Both	680 (606, 752)	644.06 (521.18, 768.90)	96 (81, 113)	59.72 (46.87, 75.74)	−44.56	−6.93 (−7.30, −6.56)	−55.6	−10.54 (−11.05, −10.02)	−20.71	−7.41 (−7.89, −6.93)	−16.72	−7.89 (−9.90, −5.84)	−85.93	−8.27 (−8.51, −8.02)
YLDs														
Male	39 (26, 52)	78.47 (50.9, 111.63)	27 (18, 37)	34.28 (22.17, 48.96)	−4.81	−2.08 (−2.35, −1.81)	−12.53	−3.26 (−3.61, −2.92)	−12.79	−4.64 (−4.90, −4.38)	4.75	−0.06 (−6.72, 7.08)	−29.5	−2.98 (−3.21, −2.75)
Female	23 (15, 32)	45.84 (29.22, 65.72)	14 (9, 19)	18.83 (12.32, 27.01)	−14.53	−2.99 (−3.46, −2.51)	−23.28	−4.39 (−5.06, −3.71)	−4.11	−1.84 (−2.10, −1.58)	2.86	−0.08 (−6.76, 7.09)	−40.16	−3.5 (−3.65, −3.35)
Both	61 (41, 83)	62.54 (40.32, 89.22)	41 (27, 55)	26.74 (17.36, 38.25)	−8.43	−2.4 (−2.47, −2.34)	−16.24	−3.63 (−4.08, −3.18)	−10.03	−3.73 (−3.94, −3.51)	4.11	−0.07 (−6.73, 7.08)	−33.47	−3.16 (−3.33, −2.99)
DALYs														
Male	449 (388, 508)	867.23 (720.89, 1016.53)	97 (80, 117)	119.95 (97.60, 145.83)	−37.96	−6.14 (−6.57, −5.70)	−45.78	−8.64 (−9.09, −8.19)	−17.6	−6.38 (−6.75, −6.01)	−11.47	−5.8 (−9.14, −2.34)	−78.37	−6.88 (−7.07, −6.69)
Female	292 (244, 332)	538.1 (433.96, 641.67)	39 (32, 48)	51.34 (40.73, 65.02)	−47.12	−7 (−7.31, −6.70)	−58.39	−10.8 (−11.22, −10.38)	−19.47	−6.77 (−7.28, −6.25)	−11.29	−5.57 (−9.06, −1.95)	−86.54	−8.43 (−8.70, −8.16)
Both	741 (661, 815)	706.6 (580.85, 833.58)	136 (117, 161)	86.46 (69.84, 106.39)	−41.57	−6.45 (−6.78, −6.11)	−50.21	−9.33 (−9.76, −8.90)	−18.15	−6.49 (−6.84, −6.14)	−11.42	−5.73 (−9.11, −2.23)	−81.59	−7.39 (−7.59, −7.19)

Note: N: Number of person−years×10,000. P′: Change in number (%). Indicators: ASR; YLLs; YLDs; DALYs.

Abbreviations: EAPC=estimated annual percentage change; UI=uncertainty interval; CI=confidence interval; ASR=age-standardized rate; TB=Tuberculosis; YLLs=years of life lost; YLDs=years lived with disability; DALYs=disability-adjusted life years.

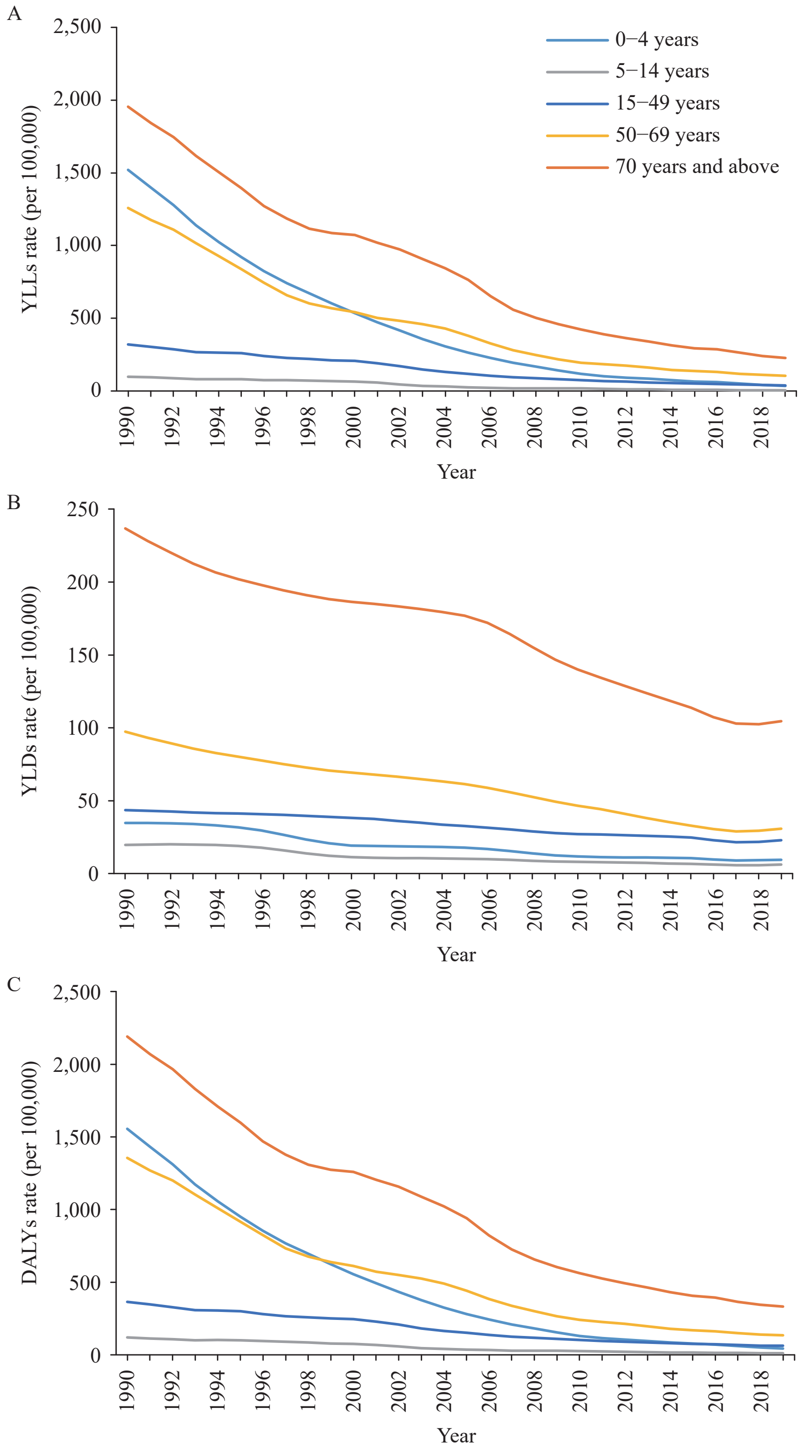

FIGURE 2. The rate of disease burden caused by TB in China by age group from 1990 to 2019. (A) TB related YLLs; (B) TB related YLDs; (C) TB related DALYs.

Abbreviations: TB=Tuberculosis; YLLs=years of life lost; YLDs=years lived with disability; DALYs=disability-adjusted life years.

1990 to 2019. The average annual ASRs decreased by 8.27%, 3.16%, and 7.39%, and the number of person-years decreased by 85.93%, 33.47%, and 91.59%, respectively. The decrease of YLDs was relatively small. In the ASR of DALYs, YLLs and YLDs accounted for 91.22% and 8.78% in 1990, and 69.07% and 30.93% in 2019.

The segmented quantitative analysis showed that only the YLDs from 2016 to 2019 had a steady trend, while the others showed a downward trend. YLLs, YLDs, and DALYs all had the largest decline from 2001 to 2010. The ASRs decreased by 10.54%, 3.63%, and 9.33% annually, and the number of person-years decreased by 55.60%, 16.24%, and 50.21%, respectively. The decline was the smallest from 2016 to 2019. The number of YLLs and DALYs decreased by 16.72% and 11.42%, respectively, while the number of YLDs increased by 4.11%.

The burden of men is about twice that of women with ASRs always higher than that of women and both sexes combined. The decline of the three indicators in women was higher than that in men at different time intervals, except that the decline of YLDs in men was higher from 2011 to 2019. According to Figure 2, the rates of the three indicators decreased significantly in all age groups, especially YLLs. The group ≥70 years old had the heaviest burden, followed by the group of 50–69 years old, and the group under 15 years old had always been the lowest. The gap in YLLs rates of all age groups gradually shrank.

DISCUSSION

In 2019, DALYs caused by TB in China were estimated at 1.36 million per year, and the ASR was 86.46 per 100,000 population. The disease burden for men was higher than that of women, and the downward trend for women was faster. The highest burden was in the elderly population. This was similar to the demographic characteristics of the prevalence and incidence of TB (*2*). In 1990–2019 years, the age standardized rate of DALYs decreased significantly (−7.39%). The national TB control plan implemented during the period effectively curbed the epidemic situation of tuberculosis and improved the equity and accessibility of prevention and treatment services (*7*).

DALYs decreased the most from 2001 to 2010 (ASR decreased by 9.33% and quantity decreased by 50.21%). The core of the two prevention and control plans implemented from 1991 to 2010 was to gradually implement the directly observed treatment of short course strategy (DOTS) and complete the coverage nationwide in 2005. The subsequent maximum decline reflects the effectiveness of DOTS in TB control. Effective control was also achieved from 2011 to 2015. The establishment of a service system with clear divisions of labor, coordination, and cooperation among disease control, medical and grass-roots medical and health institutions played vital roles. The number of DALYs dropped only 11.42% between 2016 and 2019, while the magnitude of change in ASR was similar (−5.73 *vs*. −6.45 *vs*. −6.49). This indicated a substantial reduction in the number of patients, but the rebound in YLDs necessitates attention.

The magnitude of the decline was larger than that of the United States, India, Japan, and the global level, but the burden was still higher than that of the United States and Japan (*8*). The composition of DALYs and YLLs were much higher than YLDs. In particular, there was a ten-fold drop in 1990 while the difference in 2019 was two-fold. This shows that the burden of TB in China was mainly caused by premature death, which is consistent with the situation in other parts of the world (*8*). However, the proportion of premature deaths decreased significantly, reflecting the therapeutic effectiveness of anti-TB drugs. The decline of YLDs is relatively small, indicating that the disability burden caused by TB needs targeted control measures. This is related to the characteristics of TB, such as the long treatment cycle.

This study was subject to some limitations. First, the GBD study used Japanese life expectancy as estimated value, which partly exaggerated the YLL caused by TB in China. Second, it cannot reflect the specific situation of pulmonary TB or the situation in other regions.

In summary, over the past few decades, the disease burden of TB has been decreasing, but remains high. Administrative regions at all levels must enhance government commitment, especially in high-risk areas (*1*,*7*,*9*). TB prevention and treatment institutions should strengthen research and apply DALYs to comprehensively evaluate the health damage caused by TB.

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Corresponding author: Hongyan Yao, yaohy@chinacdc.cn.

1 Chinese Center for Disease Control and Prevention, Beijing, China.

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Vital Surveillances

A Time-Series Analysis on the Association Between Fine Particulate Matter and Daily Mortality — Shijiazhuang City, Hebei Province, China, 2015–2020

Mingyang Guan[1,2,&]; Chengyao Sun[3,&]; Dajing Tang[3]; Hui Kang[1,2]; Fengge Chen[1,2,#]

ABSTRACT

Introduction: Shijiazhuang is one of the most polluted cities in China, but few studies have investigated the acute impact of fine particulate matter ($PM_{2.5}$) on mortality in this city. We assessed associations between $PM_{2.5}$ and cause-specific mortality during 2015 to 2020.

Methods: We obtained air quality data from Shijiazhuang Ecology and Environment Bureau, meteorological data from Shijiazhuang Meteorological Bureau, and mortality data from Shijiazhuang CDC's Cause of Death Reporting System for our analyses. We used a quasi-Poisson regression generalized additive model to assess excess risk of death for a single time-lag and for moving average time-lags of 0–7 days, stratifying by year, sex, age, and education.

Results: There were 76,859 non-accidental deaths recorded in Shijiazhuang during the study period. The daily concentration of $PM_{2.5}$ ranged from 6.3 μg/m^3 to 625.3 μg/m^3, and the annual mean concentration was 77.6 μg/m^3. Regression analysis showed that an increment of $PM_{2.5}$ of 10 μg/m^3 in a two-day average concentration (lag01) was associated with 0.47% [95% Confidence Interval (CI): 0.24%, 0.70%], 0.49% (95% CI: 0.19%, 0.79%), and 0.72% (95% CI: 0.22%, 1.23%) increases in non-accidental deaths, cardiovascular disease deaths, and respiratory disease deaths, respectively. With reduction of $PM_{2.5}$ concentration, impact of $PM_{2.5}$ on respiratory disease deaths decreased, but the impact of $PM_{2.5}$ on total non-accidental deaths and circulatory disease deaths did not change significantly.

Conclusion: Although $PM_{2.5}$ has been greatly reduced in recent years, $PM_{2.5}$ pollution is still serious in Shijiazhuang. $PM_{2.5}$ was significantly associated with non-accidental death, cardiovascular disease death, and respiratory disease death. As $PM_{2.5}$ concentrations decreased, risk of death from respiratory diseases also decreased.

Air pollution is a major environmental risk factor affecting health worldwide. According to the World Health Organization, more than 4 million people die prematurely every year due to outdoor air pollution(*1*). The relationship between fine particulate matter ($PM_{2.5}$) and mortality has been evaluated worldwide, in China, and in multiple-city studies (*2*–*4*). Evidence is accumulating showing regional differences in health response to air pollution. For example, the impact of $PM_{2.5}$ on mortality varies greatly by country, region, and climate characteristics. Hebei Province's capital, Shijiazhuang, is situated in the heart of the North China Plain and the Beijing-Tianjin-Hebei regional city cluster, and is one of the most polluted cities in China (*5*). We analyzed the most recent and longest time series data available, spanning the years 2015 to 2020, to explore the relation between $PM_{2.5}$ and cause-specific mortality and to identify $PM_{2.5}$-related sensitive illnesses and vulnerable populations. We determined the shapes of $PM_{2.5}$ exposure-response curves and explore how $PM_{2.5}$ and its health risks have changed in recent years in Shijiazhuang through environmental pollution control measures such as the "Blue Sky Protection Campaign," improvements in energy, heating, transportation and land use, and improvements in polluting small enterprises.

METHODS

The study obtained daily mortality data from January 1, 2015, to December 31, 2020 from Shijiazhuang CDC's Cause of Death Reporting System. Causes of death were classified according to the International Classification of Diseases, 10th revision (ICD-10) (*6*), including total non-accidental causes ("ALL", codes A00-R99), cardiovascular disease ("CVD", codes I00-I99), and respiratory diseases ("RESP", codes J00-J99). We categorized non-accidental deaths into strata by sex, age group (5–64 years and 65 years or older), and education level (low:

less than or equal to 9 years of education; high: more than 9 years of education). Deaths of children five years and under were too few to analyze and were excluded. Meteorological factors (daily average temperature and relative humidity) and air pollution data [daily 24-hour average concentration of $PM_{2.5}$, particulate matter with particle size below 10 microns (PM_{10}), SO_2, and NO_2, and maximum eight-hour mean concentration of O_3] were obtained from Shijiazhuang Meteorological Bureau and Shijiazhuang Ecology and Environment Bureau, respectively.

We examined associations between $PM_{2.5}$ and cause-specific mortality using generalized additive models (GAM) (*7*) with a quasi-Poisson link function to account for over-dispersion of daily cause-specific deaths. We controlled for seasonal patterns, long-term trends, temperature, and relative humidity using natural cubic regression smoothing. Our analyses allowed 7 degrees of freedom (*df*) per year for time long-term trends, 6 *df* for daily mean temperature, and 3 *df* for daily mean relative humidity, to minimize the Akaike's Information Criterion (AIC) value of GAM. We stratified analyses by year (2015–2017 and 2018–2020).

The description of the model, methods and results for analyses of different periods (2015–2017 and 2018–2020) as shown in Supplementary Table S1 (available in http://weekly.chinacdc.cn/), Spearman's correlation coefficients as shown in Supplementary Table S2 (available in http://weekly.chinacdc.cn/), sensitivity analyses as shown in Supplementary Table S3 (available in http://weekly.chinacdc.cn/), two-pollutant models as shown in Supplementary Table S4 (available in http://weekly.chinacdc.cn/), and stratification analyses were presented in the Supplementary materials. Analyses were conducted using the packages "mgcv" in R statistical software (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria). We used two-tailed tests; *P* values less than 0.05 were considered statistically significant.

RESULTS

Table 1 showed mortality, $PM_{2.5}$, and meteorological data and daily average counts of non-accidental (ALL), cardiovascular (CVD), and respiratory (RESP) deaths. During the study period, there were averages of 35 ALL, 19 CVD, and 5 RESP deaths per day. Among the 76,859 ALL deaths, there were 41,473 (54.0%) CVD deaths and 9,955 (13.0%) RESP deaths. Daily concentration of $PM_{2.5}$ ranged from 6.3 μg/m^3 to 625.3 μg/m^3, and the annual-mean concentration was 77.6 μg/m^3. There were 767 days (35% of the study period days) in which $PM_{2.5}$ concentration was over 75 μg/m^3, the national second ambient air quality standard in China. As shown in Supplementary Table S1, $PM_{2.5}$ pollution was lower during 2018 to 2020 compared with 2015 to 2017, as the $PM_{2.5}$ average concentration decreased from 91.1 μg/m^3 to 64.1 μg/m^3, while the maximum concentration decreased from 625.3 μg/m^3 to 355.0 μg/m^3 and the number of days exceeding the national standard decreased from 480 to 287 days.

As shown in Figure 1, the delayed effects of $PM_{2.5}$ on ALL mortality were statistically significant for lag1, lag2, lag01, lag02, lag03, and lag04; the largest delayed effects estimates were for lag01, in which a 10 μg/m^3 increase in $PM_{2.5}$ was associated with an increment in ALL deaths of 0.47% (95% CI: 0.24%, 0.70%). For

TABLE 1. Daily mortality, $PM_{2.5}$, and meteorological data in Shijiazhuang, 2015–2020.

Variable	Mean (SD)	Min	P_{25}	P_{50}	P_{75}	Max
Daily mortality						
ALL	35 (10)	12	28	34	41	107
CVD	19 (7)	4	14	18	23	67
RESP	5 (3)	0	3	4	6	31
Air pollutant (μg/m^3)						
$PM_{2.5}$	77.6 (67.9)	6.3	35.0	56.0	94.5	625.3
Weather conditions						
Average temperature (℃)	14.8 (10.8)	−10.2	4.6	16.0	24.6	33.7
Relative humidity (%)	55.5 (20.3)	7	39	55	72	100

Abbreviations: ALL=total non-accidental mortality from all causes; CVD=cardiovascular disease; RESP=respiratory disease; $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; SD=standard deviation; Min=Minimum; P_{25}=the 25th percentile; P_{50}=the median; P_{75}=the 75th percentile; Max=Maximum.

CVD mortality, the delayed effects of $PM_{2.5}$ were statistically significantly for lag1, lag2, lag01, lag02, lag03, lag04, and lag05; the largest delayed effects estimates were also for lag01, with a 10 μg/m^3 increase in $PM_{2.5}$ corresponding to a 0.49% (95% CI: 0.19%, 0.79%) increment in death. For RESP mortality, in single-day lag models, significant associations were limited to the first day after $PM_{2.5}$ exposure, with a 10 μg/m^3 increase in $PM_{2.5}$ corresponding to a 0.78% (95% CI: 0.33%, 1.23%) increment in death. When $PM_{2.5}$ exposures were lagged over multiple days, the associations were strongest for exposures during lag01 (Estimates: 0.72%, 95% CI: 0.22%, 1.23%).

For Figure 2A and 2B, the exposure-response curves for ALL and CVD showed increasing trends. When $PM_{2.5}$ concentrations were lower than 120 μg/m^3 or higher than 300 μg/m^3, slopes of curves showed marked increases. When $PM_{2.5}$ concentrations were between 120 μg/m^3 and 300 μg/m^3, slope was flat. In Figure 2C, the exposure-response curve for respiratory mortality was nearly linear and positive. When $PM_{2.5}$ concentration was over 300 μg/m^3, confidence intervals were wider than when $PM_{2.5}$ concentration was less than 300 μg/m^3.

As shown in Table 2, compared with 2015–2017, during 2018–2020, the effect of $PM_{2.5}$ on ALL mortality was larger, and the estimated effect value changed from 0.50% to 0.63%, but the difference was not statistically significant. The effect on CVD mortality was slightly less and not statistically significantly different. The effect of $PM_{2.5}$ on RESP mortality was significantly less and was statistically significantly different. The association between $PM_{2.5}$ and total mortality varied by demographic characteristics. Throughout the 2015–2020 study period, an increase in $PM_{2.5}$ of 10 μg/m^3 corresponded to a 0.53% increment in deaths of males and a 0.39% increment in deaths of females. The

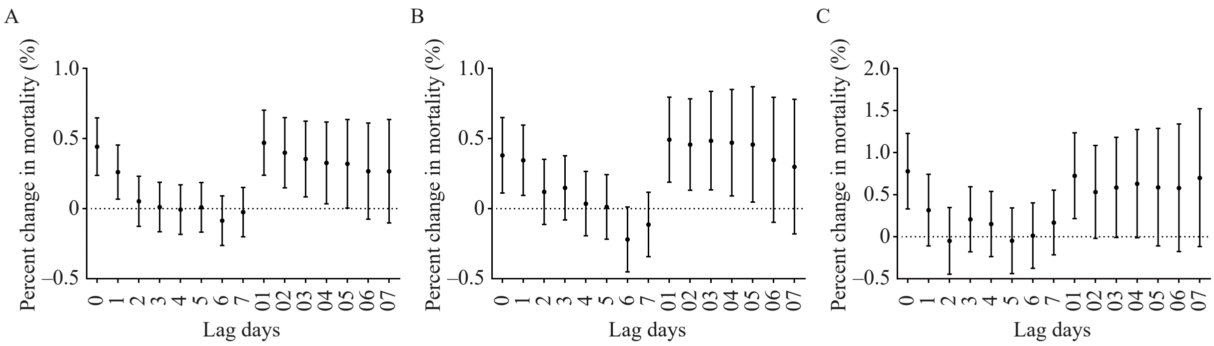

FIGURE 1. Percent changes (95% CI) in daily cause-specific mortality per 10 μg/m^3 increase in $PM_{2.5}$ concentrations using different lag days; (A) ALL mortality, (B) CVD mortality, (C) RESP mortality.

Abbreviations: ALL=total non-accidental death; CVD=cardiovascular disease; RESP=respiratory disease; $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm.

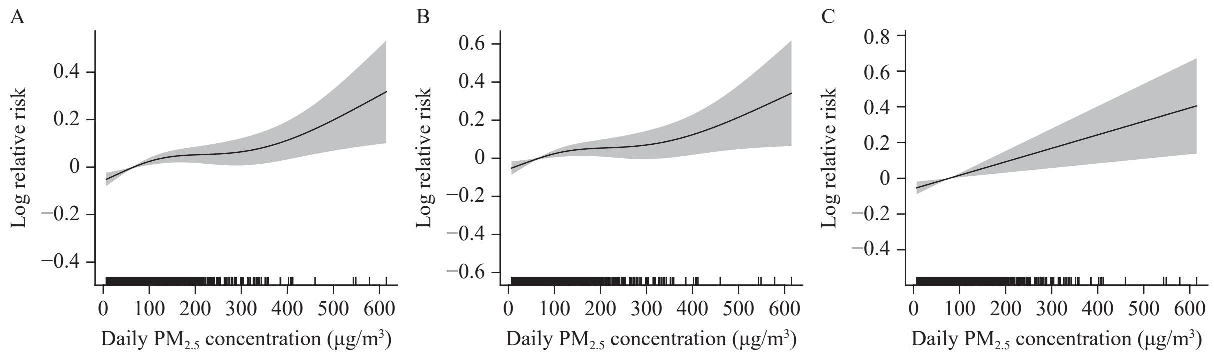

FIGURE 2. Exposure-response curves for associations of daily $PM_{2.5}$ concentrations (lag 01) with (A) ALL mortality, (B) CVD mortality, and (C) RESP mortality.

Notes: The y-axis can be interpreted as the relative change from the mean effect of $PM_{2.5}$ on mortality. The solid lines represent mean estimates, and the shaded areas represent 95% confidence intervals.

Abbreviations: ALL=total non-accidental death; CVD=cardiovascular disease; RESP=respiratory disease; $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm.

TABLE 2. Percent change (95% CI) in daily cause-specific mortality and total non-accidental mortality stratified by sex, age, and educational level per 10 μg/m^3 increase in concentration of $PM_{2.5}$ in different time periods.

Different groups	2015–2020 (Lag01)	2015–2017 (Lag01)	2018–2020 (Lag0)
Cause-Specific mortality			
ALL	0.47 (0.24, 0.70)	0.50 (0.23, 0.78)	0.63 (0.26, 1.01)
CVD	0.49 (0.19, 0.79)	0.65 (0.28, 1.01)	0.60 (0.12, 1.08)
RESP	0.72 (0.22, 1.23)	0.94 (0.32, 1.56)	−0.15 (−0.99, 0.70)*
Sex			
Man	0.53 (0.25, 0.81)	0.58 (0.25, 0.91)	0.60 (0.12, 1.08)
Woman	0.39 (0.07, 0.70)	0.39 (0.01, 0.78)	0.69 (0.18, 1.20)
Age (years)			
5–64	0.51 (0.09, 0.93)	0.63 (0.13, 1.14)	0.54 (−0.16, 1.25)
≥65	0.47 (0.22, 0.72)	0.47 (0.17, 0.78)	0.67 (0.27, 1.07)
Education level			
Low	0.51 (0.25, 0.78)	0.57 (0.25, 0.89)	0.67 (0.23, 1.10)
High	0.37 (0.02, 0.72)	0.37 (−0.07, 0.81)	0.56 (−0.01, 1.12)

Notes: Educational level: low, ≤9 years of education; high, >9 years of education.

Abbreviations: ALL=total non-accidental mortality from all causes; CVD=cardiovascular disease; RESP=respiratory disease.

* P<0.05 *vs.* 2015–2017.

5–64-year-old group and ≥65-year-old-group had similar mortality associations. The association between $PM_{2.5}$ and total mortality was a 0.51% increment for people with lower educational achievement and a 0.37% increment for those with higher educational achievement. There were no statistically significant differences among sex, age, and education in stratified analyses.

DISCUSSION

During the study period, $PM_{2.5}$ pollution in Shijiazhuang improved compared with previous years (*8*), but pollution was still serious. Our general additive model results showed that ALL mortality, CVD mortality, and RESP mortality were related to $PM_{2.5}$ concentration. Sensitivity analysis and 2 pollutant models indicated that $PM_{2.5}$ had an independent health effect on ALL mortality, CVD mortality, and RESP mortality.

Whether improvement of $PM_{2.5}$ can reduce mortality is still controversial. During the study periods of 2015–2017 and 2018–2020, after the concentration of $PM_{2.5}$ was reduced, the most direct manifestation of the reduction was a significant decrease in RESP mortality. The respiratory system is a target organ of $PM_{2.5}$ direct action, and $PM_{2.5}$ concentration is directly related to the occurrence and development of respiratory diseases. With improvement of people's health awareness, residents wear masks and use air purifiers on polluted days. No significant change was observed for ALL mortality and CVD mortality. Due to its small particle size, $PM_{2.5}$ can enter the blood circulation through the gas-blood barrier, thus affecting the circulation system, in which the composition of $PM_{2.5}$ plays a major role. $PM_{2.5}$ components should be further analyzed in the future to find harmful components and take targeted control measures.

ALL mortality in our study consisted mainly of circulatory system diseases, tumors, respiratory system diseases, endocrine and metabolic diseases, and digestive system diseases. In addition to circulatory system diseases and respiratory system diseases, the connection between other system diseases and $PM_{2.5}$ needs to be explored in future studies.

The effect values we observed differed slightly from those observed in previous studies. There is significant spatial heterogeneity between $PM_{2.5}$ concentration and daily mortality in different countries and regions (*2*,*9*). Our study found that every 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with a 0.47% increase in ALL mortality — a value that was higher than results of a recent study of 272 cities in China (0.22%) (*3*). Many factors may be responsible for the difference, including different $PM_{2.5}$ components, long-term air pollution levels, and population susceptibility. The larger effect estimates observed in our study may also be due to higher $PM_{2.5}$ concentrations.

The shape of the exposure-response curves was linear without discernible thresholds, which was consistent with findings from previous studies (*10*). As shown in our study and a previous multisite study of 272 representative cities in China, there was a marked increase in E-R values at lower $PM_{2.5}$ levels and a leveling off at relatively high concentrations (*3*). The stability observed at higher concentrations may be the result of a "harvesting effect," since susceptible populations may die before air pollutant concentrations reach very high levels (*11*). When $PM_{2.5}$ concentrations were above 300 μg/m^3, slopes of the curves markedly increased. Therefore, reducing outdoor activity on heavily polluted days may reduce risk of death. Associations of $PM_{2.5}$ on RESP mortality for $PM_{2.5}$ concentrations over 300 μg/m^3 were characterized by wider confidence intervals, implying that the mortality risk has greater uncertainty.

When stratified by sex, age, and educational attainment, we found higher association in males, 5–64-year-olds, and individuals with lower educational achievement, but differences between sex, age group, and education were not statistically significant in stratified analyses. These findings may be due to occupational factors, as young men with low education levels may engage in more outdoor work, resulting in exposure to higher concentrations of air pollution. Lin et al. (*12*) found that older people may be more susceptible to $PM_{2.5}$ in 6 cities of the Pearl River Delta region. Lee et al. (*13*) found that the most vulnerable population in three southeastern states was people with low educational achievement. A study in Shenzhen showed a high effect of $PM_{2.5}$ on males and the elderly (*14*), whereas an analysis from 160 communities of China showed females, older individuals, and widows appeared to be more vulnerable to $PM_{2.5}$ (*9*). There were differences in lifestyle, physiological factors, immunity, housing, and medical conditions by sex, age, and education, all of which can lead to different research results. Identification of potentially susceptible populations is crucial to public health and to the development of targeted intervention strategies.

This study was subject to some limitations. First, we used pollutant concentration data from urban environmental monitoring stations instead of population exposure concentrations. People spend much of their time indoors, and there is a significant difference between indoor and outdoor pollution (*15*). Therefore, there will be differences between our results and the real effects of $PM_{2.5}$. Second, the primary causes of death were categorized into circulatory and respiratory diseases. Categorization should be further refined to screen out sensitive diseases. Finally, our research only analyzed Shijiazhuang, which has relatively high pollution levels, thus, caution should be exercised when generalizing these findings to other locations.

Our findings showed an effect of air pollution on mortality in Shijiazhuang and emphasized the necessity of further controlling $PM_{2.5}$ and continuing the significant achievements in $PM_{2.5}$ control that have been made in Shijiazhuang. Futher studies on associations of components of $PM_{2.5}$ with cause-specific mortality are still needed to guide environmental health policies to improve population health.

Conflicts of Interest: No conflicts of interest.

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[#] Corresponding author: Fengge Chen, chenfengge319@163.com.

[1] Shijiazhuang Center for Disease Control and Prevention, Shijiazhuang, Hebei, China; [2] Research Base for Environment and Health in Shijiazhuang, Chinese Center for Disease Control and Prevention, Shijiazhuang, Hebei, China; [3] North China University of Science and Technology, Tangshan, Hebei, China.
[&] Joint first authors.

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Supplementary Material

Overall Summary Descriptive

During the study period of 2015–2017 and 2018–2020, the total number of non-accidental deaths increased from 31 to 39, with an increase of 8 in total deaths, including an increase of 6 deaths from circulatory diseases (from 16 to 22) and an increase of one death from circulatory diseases (from 4 to 5) (Supplementary Table S1). The annual average concentration of fine particulate matter ($PM_{2.5}$) decreased from 91.1 μg/m^3 to 64.1 μg/m^3, a decrease of 29.64%, but still exceeded the annual average concentration limit (the secondary limit of 35 μg/m^3 in China and 10 μg/m^3 in WHO). Temperature and humidity remained stable.

Spearman's Correlation Coefficients

As show in Supplementary Table S2, the relationship between $PM_{2.5}$ and four pollutants or two meteorological

SUPPLEMENTARY TABLE S1. Overall summary descriptive statistics of daily mortality, $PM_{2.5}$ and meteorological data in Shijiazhuang for two periods (2015–2017 and 2018–2020).

Variable	Period	Mean (SD)	Min	P_{25}	P_{50}	P_{75}	Max
Daily mortality							
ALL	2015–2017	31 (8)	12	25	30	36	69
ALL	2018–2020	39 (10)	17	32	38	44	107
CVD	2015–2017	16 (5)	4	12	16	19	43
CVD	2018–2020	22 (7)	6	17	21	25	67
RESP	2015–2017	4 (2)	0	3	4	6	31
RESP	2018–2020	5 (3)	0	3	5	6	16
Air pollutant (μg/m^3)							
$PM_{2.5}$	2015–2017	91.1 (79.4)	6.3	40.3	66.2	112.0	625.3
$PM_{2.5}$	2018–2020	64.1 (50.5)	9.0	31.6	47.4	78.0	355.0
Weather conditions							
Temp (℃)	2015–2017	14.8 (10.6)	−10.2	4.6	16.1	24.4	33.2
Temp (℃)	2018–2020	14.8 (11.0)	−7.4	4.6	15.9	25.0	33.7
RH (%)	2015–2017	55.9 (20.8)	13	39	55	73	98
RH (%)	2018–2020	55.2 (19.9)	7	40	55	70	100

Abbreviations: ALL=total non-accidental mortality from all causes; CVD=cardiovascular disease; RESP=respiratory disease; $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; Temp=average temperature; RH=relative humidity; SD=standard deviation; Min=minimum; P_{25}=the 25th percentile; P_{50}=the median; P_{75}=the 75th percentile; Max=maximum.

SUPPLEMENTARY TABLE S2. Spearman correlations between air pollutants and weather conditions in Shijiazhuang from 2015 to 2020.

Variables*	PM_{10}	SO_2	NO_2	O_3	Temperature	Humidity
$PM_{2.5}$	0.92*	0.58*	0.65*	−0.33*	−0.43*	0.23*
PM_{10}		0.64*	0.72*	−0.27*	−0.38*	0.02
SO_2			0.69*	−0.23*	−0.40*	−0.35*
NO_2				−0.44*	−0.49*	−0.07*
O_3					0.80*	−0.09*
Temperature						0.13*

Abbreviations: $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; PM_{10}=particulate matter with particle size below 10 microns.

* $P<0.01$.

conditions is illustrated. Spearman's correlation coefficients between $PM_{2.5}$ and particulate matter with particle size below 10 microns (PM_{10}), SO_2, NO_2 were all positive. In contrast, the relationship between $PM_{2.5}$ and O_3 was negatively correlated. Temperature and humidity were both important factors for $PM_{2.5}$. Coefficients of −0.43 and 0.23 were observed between $PM_{2.5}$ and temperature and relative humidity, respectively.

Model Description

We controlled for the day of the week and holidays using factor variables. The model can be described as follows: *logE (Yt) = βZt + ns (time, df = 7/year) +ns (temperature, df = 6) + ns (humidity, df = 3) + as.factor (DOW) + as.factor (Holiday) + intercept*, where "*E(Yt)*" is the expected cause-specific death numbers on day t, "β" represents the logrelated rate of cause-specific mortality associated with a unit increase of $PM_{2.5}$, "*df*" represents degree of freedom ,"*DOW*" is a dummy variable for the day of the week, "*Holiday*" is a binary dummy variable for the public holiday, and "*ns*" indicates natural cubic regression smooth function. We examined the associations with different lag structures from lag0 (current day) up to lag7, as well as moving averages for the current day and the previous one to seven days: from lag01 to lag07. The exposure-response relationship curves between $PM_{2.5}$ and cause-specific mortality also were plotted.

Sensitivity Analyses and Two-Pollutant Models

We performed sensitivity analyses to assess the robustness of our estimates for the associations between $PM_{2.5}$ and cause-specific mortality. First, we changed the degrees of freedom (*df*) in the smoothness of time from 5 to 9 *df*/year. In addition, we fit two-pollutant models with adjustment for concomitant exposure to O_3.

Supplementary Table S3 summarizes the association between $PM_{2.5}$ and total non-accidental (ALL), cardiovascular (CVD), and respiratory (RESP) mortality after adjusting temporal trends by alternative degrees of freedom (5–9/year). Furthermore, although the estimates for association were changed marginally, they still remained statistically significant.

Supplementary Table S4 compared the results of the two pollutant models, after adjusting for O_3, with the results of the single pollutant models. The estimated effects of $PM_{2.5}$ on ALL, CVD, and RESP mortality remained

SUPPLEMENTARY TABLE S3. Percent change (95% CI) in ALL, CVD, and RESP mortality per 10 μg/m^3 increase in 2-day moving average concentrations of $PM_{2.5}$ (lag01) using different degrees of freedom per year.

df/year	ER (%)		
	ALL (95% CI)	CVD (95% CI)	RESP (95%*CI*)
5	0.52 (0.29, 0.75)*	0.53(0.23, 0.83)*	0.81(0.31, 1.32)*
6	0.54 (0.31, 0.78)*	0.56 (0.25, 0.86)*	0.82 (0.31, 1.33)*
7	0.47 (0.24, 0.70)*	0.49 (0.19, 0.79)*	0.72 (0.22, 1.23)*
8	0.46 (0.23, 0.69)*	0.47 (0.17, 0.77)*	0.74 (0.23, 1.25)*
9	0.47 (0.25, 0.70)*	0.50 (0.20, 0.80)*	0.73 (0.22, 1.24)*

Abbreviations: ALL=total non-accidental death; CVD=cardiovascular disease; RESP=respiratory disease; $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; *df*=degree of freedom; ER=excess risk; CI=confidence interval.
* *P*<0.05.

SUPPLEMENTARY TABLE S4. Percent change (95% CI) in ALL, CVD, and RESP mortality per 10 μg/m^3 increase in 2-day moving average concentrations of $PM_{2.5}$ (lag01) in two-pollutant models.

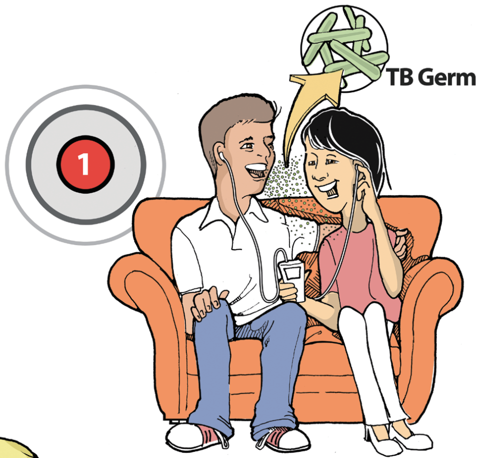
Models	ER (%)		
	ALL (95% CI)	CVD (95% CI)	RESP (95% CI)
$PM_{2.5}$	0.47 (0.24, 0.70)*	0.49 (0.19, 0.79)*	0.72 (0.22, 1.23)*
$PM_{2.5}$ + O_3	0.48 (0.24, 0.71)*	0.50 (0.19, 0.80)*	0.73 (0.22, 1.24)*

Abbreviations: ALL=total non-accidental death; CVD=cardiovascular disease; RESP=respiratory disease; $PM_{2.5}$=particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; *df*=degree of freedom; ER=Excess Risk; CI=confidence Interval.
* *P*<0.05.

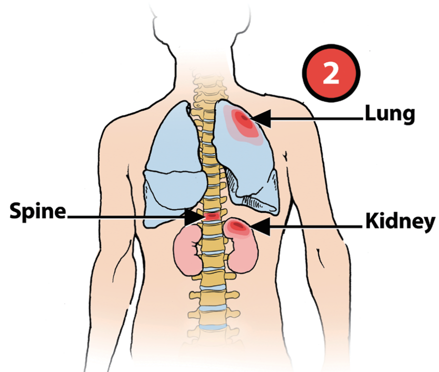
statistically significant.

Stratification Analyses

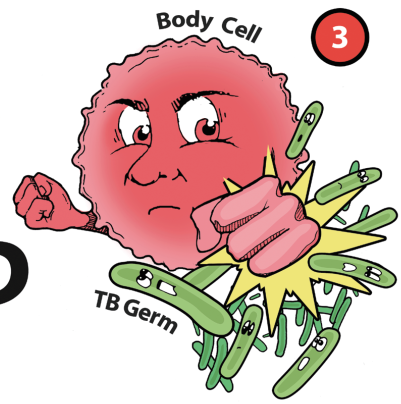
We stratified analyses by demographic factors, sex, age, and education; we tested for statistical significance of differences between effect estimates of the strata of a potential effect modifier by calculating the 95 percent confidence interval (95% CI) as $(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{(S\hat{E}_1)^2 + (S\hat{E}_2)^2}$, where $\hat{Q}_1$ and $\hat{Q}_2$ are the estimates for the two categories, $S\hat{E}_1$ and $S\hat{E}_2$ are their respective standard errors.



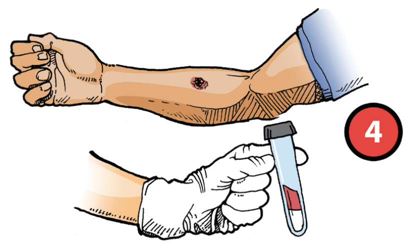
TB is spread when a person with TB disease coughs, sings, or speaks and you breathe the air contaminated with TB germs.



The germs reach your lungs. From there, they can go to other parts of your body.

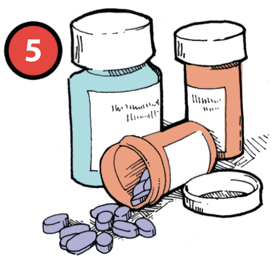


Your body fights the TB germs.

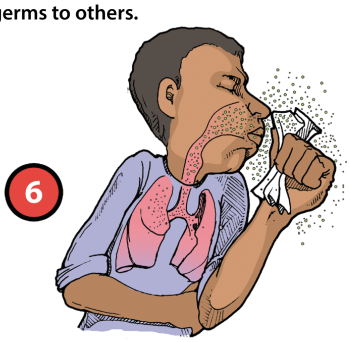


If your body controls the germs, you have LATENT TB INFECTION. When this happens,

- You may have a positive TB skin test or TB blood test.
- You don't feel sick.
- You don't have TB symptoms.
- You can't give TB germs to others.
- You have a normal chest x-ray.



You can take medicine to treat LATENT TB INFECTION and prevent getting TB DISEASE.



You get TB DISEASE when the TB germs multiply and attack your lungs or other parts of your body. When this happens,

- You have a positive TB skin test or TB blood test.
- You feel sick with cough, fever, weight loss, chest pain, or sweating at night.
- You have active TB germs in your body.
- You may give TB germs to others.
- You may have an abnormal chest x-ray.

Taking your TB medicine is very important. You need to take the medicine to help get better and to prevent the spread of TB germs to others.

STOP TB

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