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Analysis of epidemiological trends and risk factors in high-risk areas for pulmonary tuberculosis: an observational longitudinal study in Xinjiang, China

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ABSTRACT

Objective To explore the spatial and temporal variations in the long-term risk of developing tuberculosis (TB) and the factors influencing it in order to contribute to the goal of eradicating TB.

Design Observational longitudinal study.

Setting Xinjiang, China, 2005–2019.

Primary and secondary outcome measures Comparison of TB incidence across age, period, cohort and space using socioeconomic (including gross domestic product per capita, population density, public budget revenue and total retail sales of consumer goods), public health (including the number of hospital beds, health technicians and basic medical insurance for urban residents) and environmental variables (PM2.5, mean air temperature, mean wind speed, mean relative humidity and precipitation). The relative importance of these variables to pulmonary TB (PTB) is revealed by the Q-value (0, 1), with larger values indicating that the spatial heterogeneity of the explanatory variables to PTB is more pronounced.

Participants All clinically diagnosed and confirmed cases in Xinjiang, China, were collected. The descriptive analysis included confirmed cases from 2005 to 2019, while cases from various districts and counties between 2011 and 2019 were subjected to further analysis.

Results From 2005 to 2019, a total of 642 332 cases of PTB were reported in Xinjiang, with an average annual incidence rate of 172/100 000. The age risk of PTB presented a bimodal distribution, namely 20–24 years and the elderly (>60 years). The high prevalence of PTB was distributed in the southern part of Xinjiang. Among the influencing factors that had a greater effect on the incidence of PTB, the lower GDP per capita (Q-value=0.65) had a largest effect on PTB in Xinjiang compared with others factors (higher PM2.5: Q-value=0.56, lower health personnel: Q-value=0.49, higher average temperature: Q-value=0.47 and higher urban residents' health insurance: Q-value=0.46). The main influencing factors were heterogeneous in different regions. Furthermore, the interactions among these factors enhanced the explanatory power regarding the incidence of the disease.

Conclusions Identifying the high-risk groups, regions, influencing factors and interactions of PTB in Xinjiang, China, will expand the epidemiological knowledge of PTB in high-risk areas and potentially aid in designing targeted interventions.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Exploring spatial and temporal differences in the risk of long-term tuberculosis incidence.
⇒ Uses a limited number of sociodemographic variables in the analysis.
⇒ The study focused only on Xinjiang, a high-risk area in China, and did not consider other countries.

INTRODUCTION

Pulmonary tuberculosis (PTB) is a major infectious disease that seriously endangers people's health. The 2022 Global Tuberculosis Report by the WHO[1] indicates that, in 2021, there were 10.6 million newly diagnosed patients with TB globally and 780 000 in China, with an incidence rate of 55/100 000, placing our country third among the 30 high-burden TB countries. Although the incidence of TB in China has been decreasing in recent years, there remains a large gap between the 2014 WHO-proposed global 'Stop TB Strategy' and the goal of ending TB based on the TB epidemic control rate in China. Notably, the reported incidence rate in western China has been high and has been rising in recent years, with the risk of further increase in the future.[2]

Many prior studies have examined the factors influencing TB transmission. For example, a Korean study indicated that population composition ratios, population growth rates, health insurance payments and public health variables (the number of hospital beds, health personnel, etc) were significantly related to PTB incidence.[3] A retrospective study in Denmark revealed the presence of a high-risk group for PTB among men, those aged 35–65 years, those living alone and low-income individuals.[4] Furthermore, a meta-study also showed that TB morbidity and mortality were significantly associated with various climatic, socioeconomic and air quality-related factors.[5] Some studies have shown an increase in TB incidence at low wind speeds and at low wind speed-high pollutant concentration interactions.[6] The incidence of TB in the elderly in China has been reported to be two to three times higher than that in the young,[7] the nutritional status of different birth cohorts may influence the risk of TB later in life and even in future generations.[8] Nevertheless, the effects of these factors on the risk of developing PTB vary in diverse regions,[9] thus the outcomes of the study might be influenced by diverse demographic characteristics and geographical settings. It is essential to investigate the spatial and temporal patterns of PTB incidence in different regions and the influence of underlying factors.

Although Xinjiang, China, has taken a number of preventive and control measures to prevent and control the incidence and spread of TB, the number of newly reported cases of TB remains high year after year, which poses a great challenge to the country's TB prevention and control efforts. The incidence and mortality rates of TB in Xinjiang are among the highest in China.[10] Taking the entire region of Xinjiang as the study area will enhance the understanding of the epidemiology of PTB in high-risk areas. Moreover, evaluating the spatial and temporal distribution of the disease and the underlying factors is essential at both the national and provincial levels due to the diverse conditions in each region. However, relatively few studies have been conducted on the long-term spatiotemporal distribution and underlying factors of PTB across the territory, their studies have generally analysed only the trends in PTB, without in-depth analyses of possible influencing factors over time and space.[11 12] Therefore, this study had three main objectives: first, to analyse the relative risk of PTB incidence in Xinjiang by age (reflecting biological changes and social processes), period (capturing change given a specific period such as advance in medical services and health policies) and birth cohort (reflecting the unique experiences/exposures and environmental factors that the cohort has experienced during its lifetime); second, to explore the spatiotemporal heterogeneity of PTB in Xinjiang and analyse the distribution trends in the hot and cold spot areas of PTB incidence in Xinjiang; and third, to explore the influencing factors of the risk of PTB incidence in Xinjiang and the interactions between the influencing factors.

METHODS

Study area and population

Xinjiang is located in northwestern China, with a resident population of about 26 million, and is the largest provincial-level administrative region in China in terms of land area, with 4 prefectural-level cities, 5 districts, 5 autonomous prefectures and 12 county-level cities under the jurisdiction of the autonomous region, as of January 2023. The region is far from the ocean and is deeply inland, surrounded by high mountains. Far from the ocean, it is deeply inland, surrounded by high mountains, which makes it difficult for ocean air currents to reach, and is known as the 'Three Mountains and Two Basins'. Its unique geographical environment makes the region have little precipitation and a large temperature difference between day and night. There is a clear difference in climate between the northern and southern borders separated by the Tianshan Mountains, with the temperature on the southern border higher than that on the northern border and the precipitation on the northern border higher than that on the southern border. It is, therefore, important to explore the incidence of TB in this region.

Data sources

Sources of PTB cases

Data on diagnosed PTB cases in Xinjiang from January 2005 to December 2019 obtained from the Public Health China Scientific Database were descriptively analysed, and their epidemiological characteristics were analysed. All PTB cases included in this system were diagnosed according to the guidelines recommended by the Chinese Health Commission. Spatiotemporal exploratory analysis was performed using the PTB surveillance data from 2011 to 2019 from Xinjiang districts and counties provided by the Chinese Information System for Disease Control and Prevention. All clinically diagnosed and confirmed cases were included in the case classification.

Sources of influencing factors

12 socioeconomic, public health and environmental variables were considered: (1) socioeconomic, including per capita GDP, population density, public budget revenue and total retail sales of consumer goods (TRSCG); (2) public health, including the number of hospital beds, health personnel and the urban resident basic medical insurance (URBMI) and (3) environmental, including PM2.5, mean air temperature, mean wind speed, mean relative humidity and precipitation. For the purposes of this study, public budget revenues are calculated as the sum of tax revenues, non-tax revenues and grants or transfers for each fiscal year. Where tax revenues are indicated to include income, sales, property and corporate taxes collected by the government. Non-tax revenues include fees, licences and charges for services rendered by the government, as well as revenues from government-owned businesses. Grants and transfers include funds received from higher levels of government (eg, local state, city or district) or international organisations.

The above data were obtained from the Xinjiang Statistical Yearbook published by the Xinjiang Uygur Autonomous Region (https://tjj.xinjiang.gov.cn/), the China Meteorological Data Sharing Center and the National Urban Air Quality Real-time Release Platform.

Statistical analysis

This analysis used three modelling approaches to explore trends and factors influencing prevalence. First, age-period-cohort (APC) model was used to describe the trend analysis of PTB incidence in Xinjiang. Next, spatial aggregation analysis was used to explore the spatial distribution pattern of PTB in Xinjiang. Finally, a GeoDetector (GD) model was used to explore the relative importance of different influencing factors on the incidence of PTB in each space. Specific steps are described below:

Data preparation or transformations

Prior to model analysis, the data were summarised by aggregating them at intervals of five units to conform to the model requirements of the same age, period and birth cohort interval. The observation period is as long as possible to show long-term trends. According to the requirements of the APC model,[13 14] based on the study year 2005–2019 (15 years in total) for this study, the periods were categorised into three periods (2005–2009, 2010–2014 and 2015–2019), ages into 18 groups (0–4, 5–9, …, 80–84 and 85+ years) and birth cohorts (birth cohort=periodsage) into 20 groups (1920–1924, …, 2015–2019), respectively, with intervals of 5 years.

APC model

APC modelling is often used to describe trend analysis of disease incidence, and to some extent can eliminate or control for interactions between age, cohort and other factors.[15] Age effects are the accumulation of physiological changes and social experiences associated with ageing but are not related to the period to which an individual belongs or the cohort to which he or she belongs. Period effects may be caused by a range of environmental, social and economic factors, such as war, famine and economic crisis. In epidemiology, cohort effects are conceptualised as changes in interactions or effects due to influences over time or due to age-specific exposures, representing the sum of all unique exposures experienced by the cohort from birth. Our study analysed the relative risk of these three dimensions of PTB incidence trends from 2005 to 2019 using the APC model. Assuming that the number of PTB occurrences follows a Poisson distribution, the APC model can be written as:

$$ln\left(Y_{xyz}\right) = \omega + \gamma_{\dot{x}} + \delta_y + \tau_z + \vartheta_{xyz}$$

where $ln\left(Y_{xyz}\right)$is the natural logarithm of PTB incidence; $\gamma_{\dot{x}}$is the age effect for the$x$th age cohort; δ_y is the period effect for the yth period; τ_z is the cohort effect for the zth cohort group, $z = x + y - 1$; ω is the intercept and ϑ_{xyz} is the random error term. The model parameters (γ , δ , τ) were exponentially transformed to represent the relative risk (RR) for a given age, period and birth cohort relative to each average (RR>1 indicates a higher risk relative to the mean and RR<1 indicates a lower risk relative to the mean. For example, the RR of 1.74 at ages 20–24 suggests that this age group is 1.74 times more likely to report incidence than the overall mean for age during the study period.). Analyses were performed using State software (V.16.0).

Getis-Ord cold spot landscape analysis

Cold hotspot analysis is a spatial clustering method that can show the spatial aggregation and distribution pattern of high and low values of indicators, and make up for the insufficiency of spatial characterisation such as equal breakpoint grading and has been widely used in the study of spatial distribution pattern of disease.[16 17] In order to further reveal the spatial and temporal distribution pattern of PTB in Xinjiang, cold and hot spot analysis is introduced as a way to identify the cold and hot spot regions of PTB. The formula is:

$$G_i^* = \frac{\sum_j \omega_{ij} x_j - \bar{x} \sum_j \omega_{ij}}{S\sqrt{\frac{\left[n\sum_j \omega_{ij}^2 - \left(\sum_j \omega_{ij}\right)^2\right]}{n-1}}}$$

Where n is the total number of PTB incidences, $\bar{x}$is the mean, $\omega_{ij}$is the spatial weight matrix and $S$is the SD. Normally G_i^* is standardised:

$$Z\left(G_i^*\right) = \frac{G_i^* - E\left(G_i^*\right)}{\sqrt{Var\left(G_i^*\right)}}$$

Where $E\left(G_i^*\right)$ is the expected value and $Var\left(G_i^*\right)$ is the variance. The standardised G_i^* value can be used for cold hotspot identification of PTB incidence in the study area. If the standardised result $Z\left(G_i^*\right)$ is significantly positive, it means that the value around the area is higher, presenting a high value agglomeration hot spot area; if the standardised result $Z\left(G_i^*\right)$ is significantly negative, it means that the value around the area is lower, presenting a low value agglomeration cold spot area. Arcgis V.10.8 software toolbox was used to analyse the hot and cold spots.

Optimal parameters-based GD model

GD modelling is a set of statistical methods for detecting spatial heterogeneity based on the law of spatial differentiation of geographical phenomena and revealing the driving forces behind it.[18] By dividing the study area into subregions, the model compares the sum of the variances of the subregions with the variance of the region as a whole. If the former is less than the letter, the model assumes that there is spatial variation. If the spatial distributions of the two variables converge, there is a statistical correlation between them. The GD model requires the independent variables to be categorical, so it needs to discretise the independent variables. The optimal parameters-based GD model[19] used in this paper is an improvement of the GD model, with the same principle and formula, but the improvement lies in the spatial discretisation of continuous data. The model seeks to maximise the Q-value of a continuous variable through a combination of parameters with different discretisation methods (iso-intervals, natural intervals, IQ intervals, geometric intervals and SD intervals) and the number of breaks. The model is executed in the R software (V.4.3.1) using the 'GD' package.

Factor detection is the core of the GD model, which detects the spatial heterogeneity of the response variables, calculates the explanatory power of the incidence of PTB by using the variance of each spatial partition and the total variance in order to identify the main factors influencing PTB, and reveals the relative importance of the variables through the Q-value, expressed as:

$$Q = 1 - \frac{\sum_{h=1}^{m} N_h \sigma_h^2}{N\sigma^2}$$

where, h=1,…,m is the stratification of the explanatory variables, categorisation or partitioning; N_h and N are the number of PTB in stratification h and the whole area, respectively; σ_h^2 and $\sigma^2$are the variance of the response variables in stratification h and the whole area, respectively. The range of Q values is (0, 1).

Interaction testing was primarily used to identify interactions between different risk factors, that is, to assess whether factors X1 and X2, when acting together, increased or decreased the explanatory power of the dependent variable Y, or whether the effects of these factors on Y were independent of each other, and there were generally five relationships (online supplemental table S1). Each of the 12 possible influences was analysed for interaction and Q-value was used to evaluate the interaction explanatory power.

Patient and public involvement

No patients or members of the public were involved in the study.

RESULTS

Epidemiological features

From 2005 to 2019, a total of 642 332 cases of PTB were reported in Xinjiang, with an average annual incidence rate of 172/100 000. The annual incidence rate fluctuated from 2005 (163/100 000) to 2019 (169/100 000), with the highest incidence rate (299/100 000) reached in 2018 (figure 1a). Among the monthly average incidence rates, the incidence rate was higher from January to May, with an incidence rate of more than 16/100 000 (figure 1b), suggesting that winter and spring are the peak periods for the incidence of PTB in Xinjiang.

The results of the APC model showed an age effect suggesting two peak age PTB incidence rates in Xinjiang, with the second peak being approximately twice as high as the first. Ages 20–24 and 75–79 were 1.74 (95% CI 1.40 to 2.18) and 3.40 (95% CI 3.07 to 3.77) times more likely to report morbidity than the overall mean for age during the study period. The first peak is followed by a downward trend until the age of 45, after which there is an upward trend until the second peak, followed by another decline. The time effect indicated a gradual increasing trend in the risk of PTB incidence from 2005 to 2009 (RR 0.9, 95% CI 0.86 to 0.93) to 2015–2019 (RR 1.15, 95% CI 1.11 to 1.19). The birth cohort effect showed that the rest of the birth cohorts showed a lower risk of PTB development later in birth, except for 1965–1969 and 1985–1989, which showed an increasing trend. The highest risk of PTB incidence compared with the overall mean in cohort was in those born in 1920–1924 (RR 3.07,95% CI 2.51 to 3.76) and the lowest was in those born in 2015–2019 (RR 0.04,95% CI 0.01 to 0.38) (online supplemental figure S1).

Spatial and temporal distribution of PTB

From the spatial and temporal distribution map of PTB incidence rates in Xinjiang's districts and counties during 2011–2019, it can be observed that there are distinct spatial differences in the average annual incidence rates of PTB, and the incidence rates in the southern border are considerably higher than those in the northern and

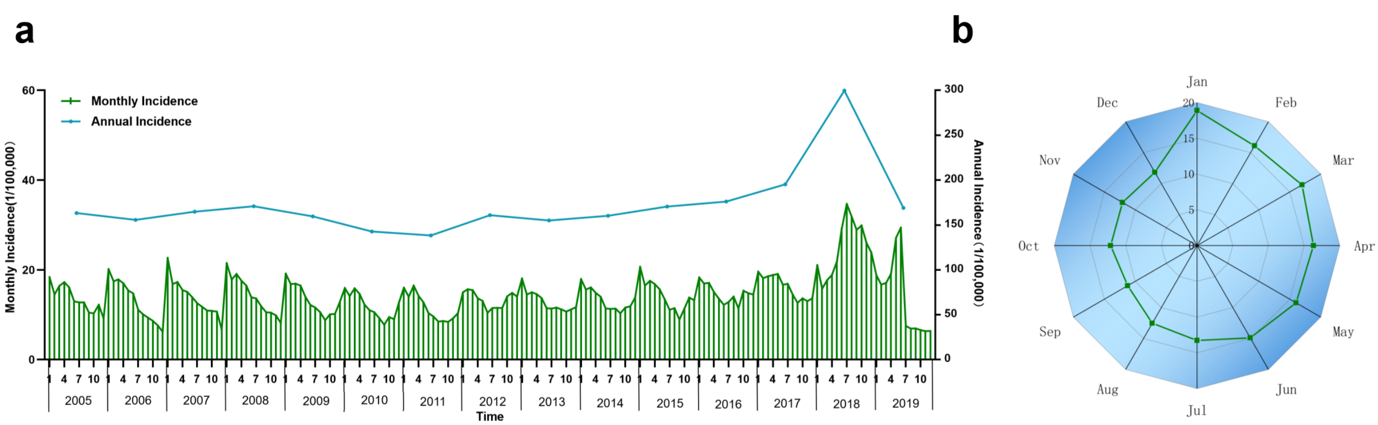

Figure 1 Temporal distribution of PTB incidence in Xinjiang, China, 2005–2019. (a) The incidence of PTB between 2005 and 2019. (b) Distribution of the monthly incidence of PTB. PTB, pulmonary tuberculosis.

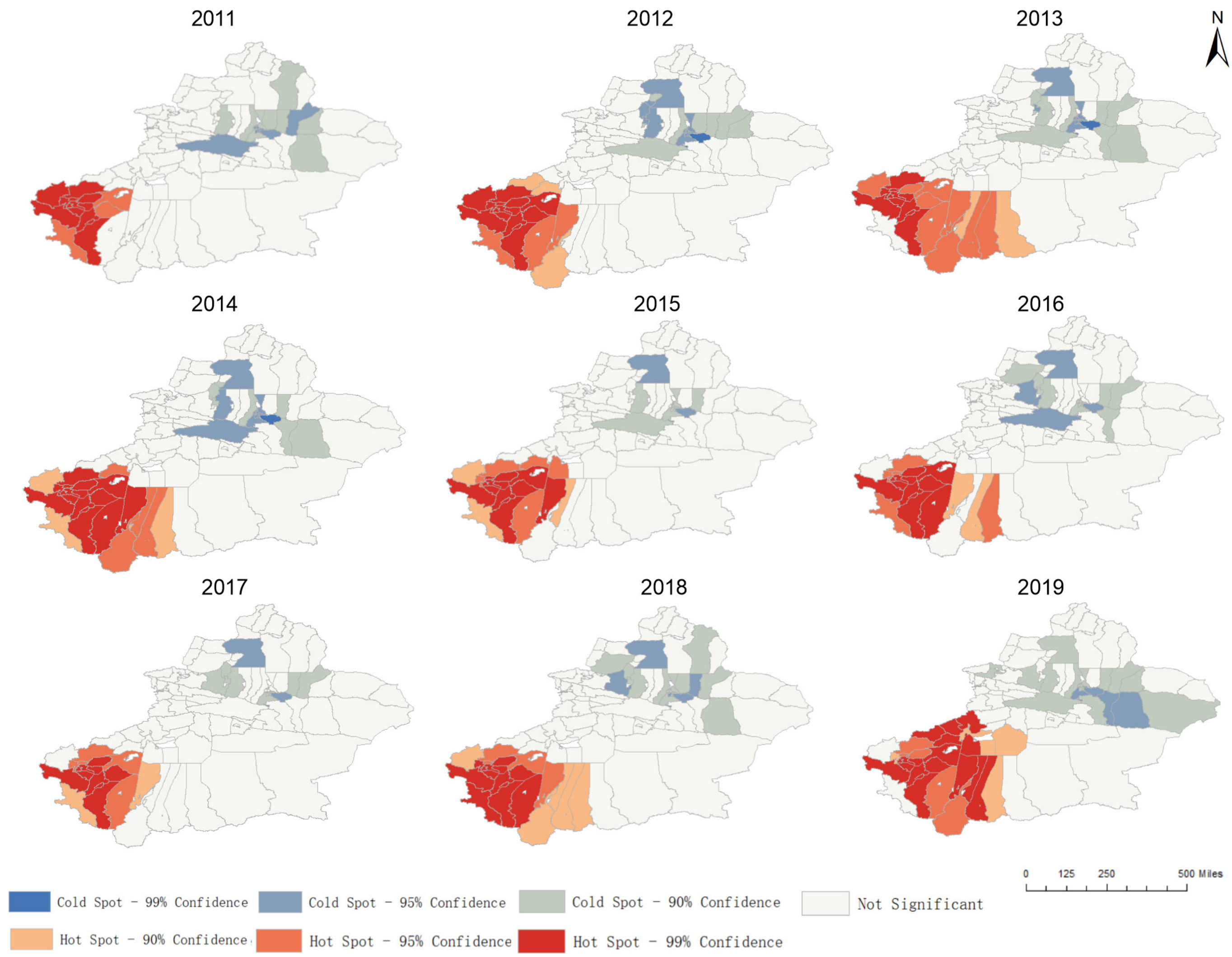

Figure 2 Distribution of hot and cold spots of PTB in Xinjiang, China, 2011–2019. PTB, pulmonary tuberculosis.

eastern borders, ranging from 9 to 1280.48 per 100 000 persons (online supplemental figure S2). During the study period, the districts and counties that showed very high incidence rates all year round (>300/100 000) were basically centred around four prefectures in southern Xinjiang, namely Kashgar, Hotan, Aksu and Kizilsu Kyrgyz Autonomous Prefecture. Especially, in 2018, there were 28 districts and counties with incidence rates of >300/100 000, of which Kashgar and Hotan districts accounted for 18 of these districts and counties.

According to the cold hotspot analysis, the incidence risk of PTB in Xinjiang from 2011 to 2019 has a very obvious spatial and temporal heterogeneity, roughly divided into the southern region as the incidence hotspot of PTB, and the northern and eastern regions as the cold spots. Especially since 2017, both cold and hot spot areas have a tendency to extend outward, with the hot spot extending from the original Kashgar region to the Hotan and Aksu regions, but still basically in the southern region. The cold spot areas extend from the northern region towards the Hami and Turpan regions in the eastern region, which may become lower-risk areas over time (figure 2).

Detection of PTB influencing factors

In this study, 12 factors were selected as explanatory variables for the incidence of PTB in Xinjiang (online supplemental table S2), including 5 environmental factors (PM2.5, average air temperature, average wind speed, average relative humidity and precipitation), 4 socioeconomic factors (GDP per capita, population density, public budget revenue and TRSCG) and 3 public health factors (number of hospital beds, number of health workers and urban residents' medical insurance), basic medical insurance for urban residents). All variables were averaged annually to assess the degree of impact on PTB incidence.

As shown in figure 3, three different levels of influencing factors all affected the incidence of PTB in Xinjiang to different degrees. The range of intervals for each influencing factor was determined by the highest maximum Q-value in the GD. The strongest explanation for the onset of PTB was GDP per capita (Q=0.65), followed by PM2.5 (Q=0.56), health technicians (Q=0.49), average

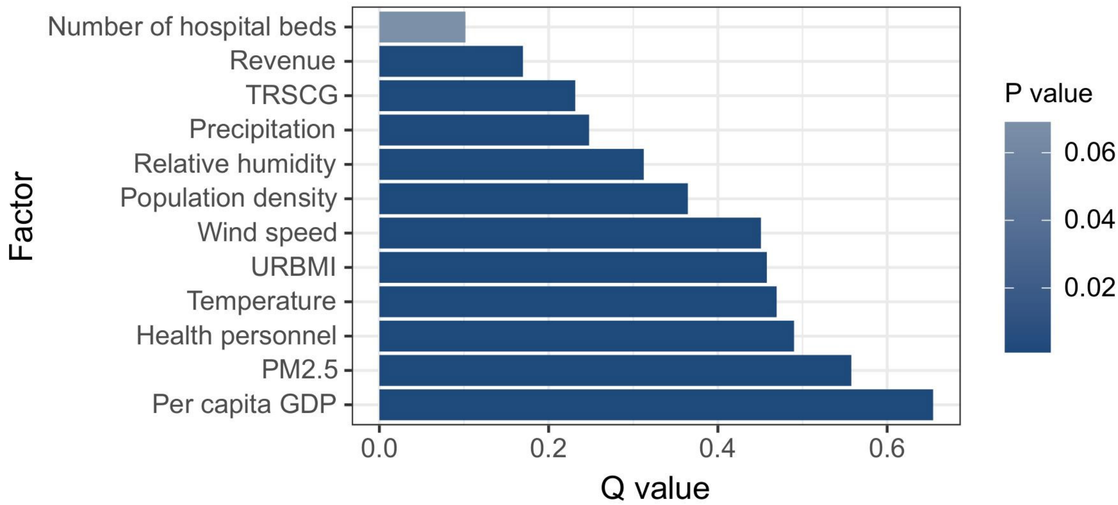

Figure 3 Determining power of factors in the spatiotemporal distribution of PTB in Xinjiang, China, 2011–2019. The shade of colour indicates the p value and the horizontal coordinate is the Q-value. GDP, gross domestic product; PTB, pulmonary tuberculosis; URBMI, urban resident basic medical insurance.

temperature (Q=0.47), urban health insurance (Q=0.46), average wind speed (Q=0.45), population density (Q=0.36), average relative humidity (Q=0.31), precipitation (Q=0.25) and social TRSCG (Q=0.23). The coefficients of determination of these variables were all greater than 0.2, indicating that these factors were strongly associated with the spatiotemporal heterogeneity of the incidence of PTB, whereas public budget revenue (Q=0.17) and the number of hospital beds (Q=0.10) had relatively little effect on the spatiotemporal distribution of PTB. In addition, all variables were statistically significant ($p<0.05$) except for the number of hospital beds (p=0.069), which was not statistically significant.

It was discovered that varied levels of individual influencing factors had diverse impacts on the onset of PTB across the region. The lower the level of socioeconomic and environmental factors of GDP per capita, public budget income, TRSCG, average wind speed, average relative humidity and precipitation, the higher the risk of PTB development. In addition, high levels of PM2.5, average air temperature, population density and health insurance for urban residents were strongly associated with high incidence of PTB (online supplemental figure S3).

As demonstrated in table 1, using the Optimal parameters-based GD model, it was revealed that there is variability in the primary factors influencing the occurrence of PTB throughout various regions throughout Xinjiang. In the southern region, population density, GDP per capita, health technicians, PM2.5 and average wind speed were the top five determinants with Q values of 0.66, 0.58, 0.57, 0.52 and 0.52, respectively, and in the northern region, the top five were GDP per capita, population density, URBMI, health personnel and PM2.5, with Q values of 0.82, 0.81, 0.63, 0.61 and 0.60. The main determinants of PTB in the eastern region were TRSCG (Q=0.72), mean temperature (Q=0.69), revenue (Q=0.68), health personnel (Q=0.63) and number of hospital beds (Q=0.56).

In addition, our findings reveal that the combination of two risk factors has a greater impact on explaining PTB in Xinjiang than any single risk factor alone. They both showed 'non-linear enhancement' and 'two-way enhancement' effects compared with their respective effects. For example, the q-value of urban residents' health insurance is 0.46, and the q values of urban residents' health insurance are 0.85

Table 1 Top five determinants and specific Q values for each region in Xinjiang, China

	Southern regions		Northern regions		Eastern regions	
Rank	Variables	Qvalue	Variables	Qvalue	Variables	Qvalue
1	Population density	0.66	Per capita GDP	0.82	TRSCG	0.72
2	Per capita GDP	0.58	Population density	0.81	Temperature	0.69
3	Health personnel	0.57	URBMI	0.63	Revenue	0.68
4	PM2.5	0.52	Health personnel	0.61	Health personnel	0.63
5	Wind speed	0.52	PM2.5	0.60	Number of hospital beds	0.56

TRSCG, total retail sales of consumer goods; URBMI, urban resident basic medical insurance.

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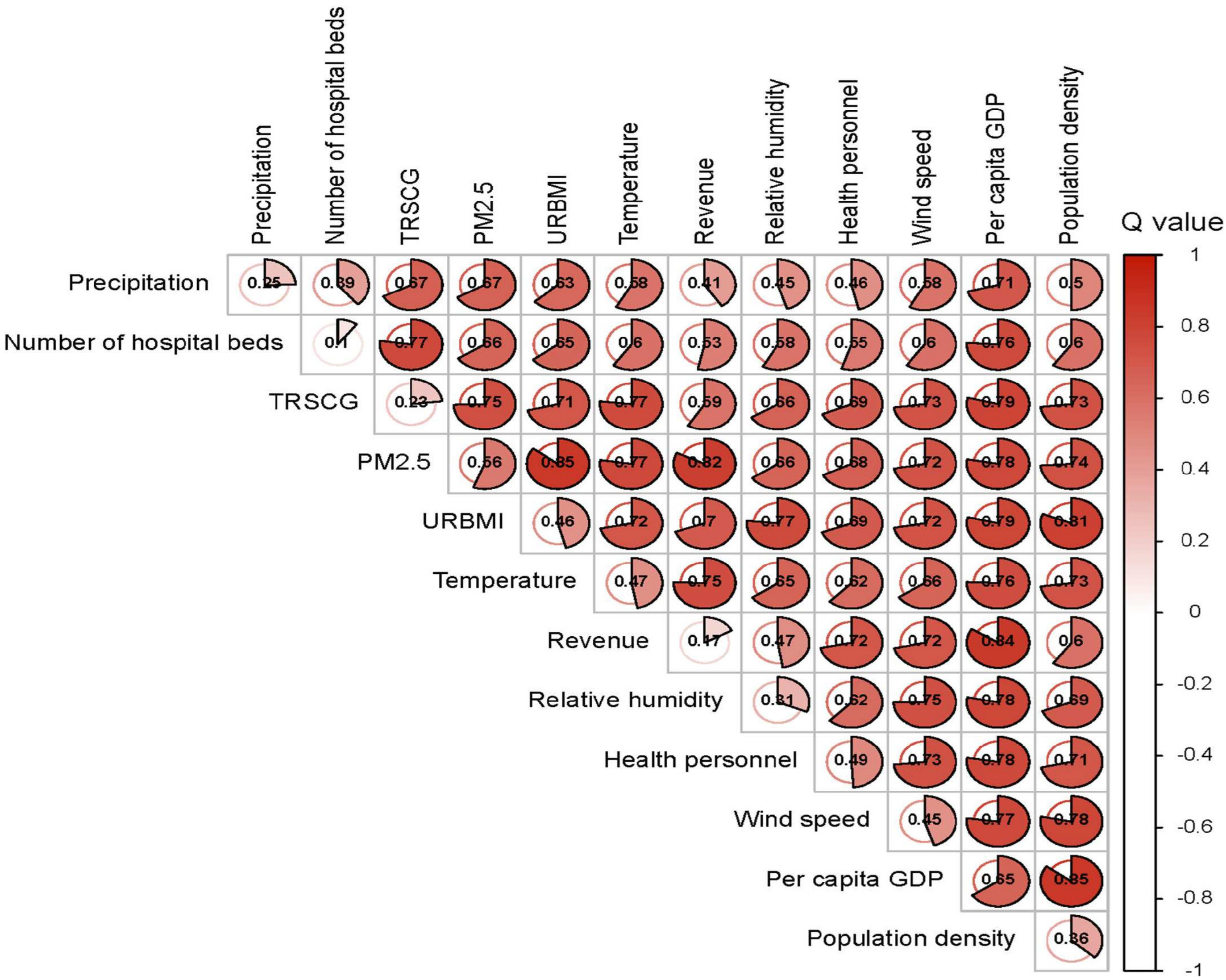

Figure 4 The Q-value of the interaction between factors in the development of PTB. GDP, gross domestic product; PTB, pulmonary tuberculosis; TRSCG, total retail sales of consumer goods; URBMI, urban resident basic medical insurance.

and 0.81 after considering the interactions of PM2.5 and population density on the incidence of TB. After considering the interaction of public budget income and total retail sales, the q-value becomes 0.84 and 0.79 (figure 4).

DISCUSSION

The results of the study are as follows: (1) We described the incidence of PTB in Xinjiang from 2005 to 2019, and the results showed that there were two peaks of incidence in the age groups, with higher risks in young people (20–24 years) and older people (>60 years). The risk of the period effect rises, and the cohort effect decreases its risk of incidence as time is delayed. (2) High-risk areas for incidence and disease hotspots were mainly concentrated in the southern region of Xinjiang. (3) GD modelling showed that PTB incidence was significantly associated with socioeconomic factors, atmospheric pollutants and public health conditions, and that there were significant differences in risk factors for PTB in different regions. The interaction of the two risk factors enhances the explanatory power for the onset of PTB compared with the individual factors.

There were fluctuations in the average annual incidence of PTB in Xinjiang from 2005 to 2019, with the highest incidence (299/100 000) in 2018 and the lowest (138/100 000) in 2011. Its incidence rate in the early period was consistent with that of most regions in China, showing a steady downward trend, which could be attributed to the implementation of a series of strategies by the government, such as DOTS,[20] which improved social, environmental and living conditions. However, we found that the period effect showed a higher risk of TB incidence in 2015–2019 (RR=1.15), similar to previous studies,[2] and the high risk of incidence in this period may be due to the implementation of universal medical checkups in Xinjiang in 2016, coupled with improved diagnostic techniques, which greatly increased the detection rate of PTB cases. In addition, we found that the average monthly incidence of TB was more than 16/100 000 during the study period from January to May. This result suggests that January–May is a high incidence period for patients with PTB, which in Xinjiang falls within the late winter and spring seasons, and this is similar to the incidence trend reported in China and other countries.[2 21 22] This may be due to the fact that ambient temperature modifies the effect of PM2.5 by altering vitamin D distribution and UV radiation,[23] and that temperatures, reduced sunlight exposure and vitamin D deficiency lead to increased incidence of TB.[6 24]

The APC model results indicate that the age effect exhibited two peaks of incidence among 18 age groups. The initial peak occurred in the 20–24 age cohort, while the second, which was approximately double the first, emerged in the 75–79 age group. It is worth noting that the risk of PTB increases significantly after the age of 60 years, suggesting that older people over the age of 60 years are also a high-risk age group for PTB. The reason for the significantly lower incidence of PTB in the age group of less than 15 years than in the other age groups may be due to the fact that the BCG vaccine is given to all newborn babies in China and the vaccine has a significant protective effect at a young age. On the other hand, there is a high rate of underdiagnosis in children.[25] The increased incidence of PTB in 20–24 years may be due to the diminished protection afforded by BCG vaccination[26] and frequent socialisation increasing the risk of transmission. In older age groups, the increased risk may be related to impaired immune function[27] and delay in seeking treatment.[28] In addition, as the birth cohort is delayed, the risk of its incidence becomes lower and lower, showing that the later the birth, the lower the risk of PTB incidence. This is related to the increased health awareness of modern people, as well as the rise in the level of medical care in the country. Both young people (20–24 years) and older people (>60 years) have a relatively high risk of PTB in China. Therefore, there is an urgent need in Xinjiang to test and treat high-risk populations and to develop a new TB vaccine.

In this study, there was significant spatial heterogeneity in the risk of PTB incidence in Xinjiang. The high incidence of PTB was mainly found in the southern part of Xinjiang (Kashgar, Hotan, Aksu and Kizilsu Kyrgyz Autonomous Prefectures), and most of them were found in areas with poor living conditions and arid climatic conditions. On the other hand, the counties with relatively low PTB prevalence were mainly located in the northern and eastern regions, which have relatively better economic and climatic conditions compared with the southern regions. These results suggest a strong association between PTB risk and uneven socioeconomic development and environmental conditions. From 2011 to 2019, there are large regional differences in the analysis of PTB incidence trends in Xinjiang in general, and through our analysis, the hotspot areas show an increasing trend, extending from Kashgar to Aksu and Hotan regions at the beginning, reminding us of the possibility of an increase in hotspot areas in the future, and we suggest that these regions should be aware of the increasing risk of PTB. Several studies have also demonstrated the distinct regional character of TB transmission.[29–31] Geospatial clustering of TB cases reflects the continued transmission or colocation of risk factors.[32]

The results of the analysis of influencing factors show that socioeconomics, environmental factors and public health conditions are the main factors influencing the spatial and temporal changes in PTB incidence. Indicators such as GDP per capita, public budget revenue and TRSCG usually represent the level of social development of a region. The study reveals that PTB transmission risk escalates as the values of these variables decline, confirming previous research.[33] Regions with superior social development may allot more resources to combat PTB. Contrarily, areas with inferior development may increase the likelihood of PTB transmission due to exposure to substandard living conditions and infrastructure. Some researchers have demonstrated that GDP has a positive effect on PTB. This may be due to the fact that higher economic levels make healthcare more accessible, contributing to the level of treatment and healthcare system, resulting in a decrease in the incidence of PTB.[34] These findings indicate a close connection between the spatiotemporal heterogeneity of PTB incidence risk and varying levels of socioeconomic development in Xinjiang.

Previous studies have emphasised a strong correlation between PTB incidence and the number of hospital beds.[34] However, in our study, we did not find a strong relationship between the number of hospital beds and PTB incidence. Instead, health technicians and URBMI had strong explanatory power, and our study supports the idea that health technicians or URBMI may influence PTB incidence. Such an influence could reduce the risk of PTB incidence through the efforts of healthcare workers or, at the socioeconomic level, through the provision of acceptable and evaluable health services and the reduction of the healthcare burden on families through health insurance.

In addition, environmental factors were important determining variables in the development of PTB in this study. There is evidence that PM2.5 is associated with inflammatory cytokines, which stimulate the overexpression of many transcription factor genes and inflammation-associated cytokine genes, thereby causing inflammatory damage, and the interaction between inflammatory cells and cytokines can synergistically damage lung cells.[35] This is consistent with our study, suggesting that areas with elevated PM2.5 levels may increase the risk of PTB development. In addition, high temperatures, low relative humidity, low wind speed and low precipitation were strongly associated with PTB incidence, suggesting that dry and warm climates may promote TB transmission. However, a study in Qinghai Province showed an increasing trend in the incidence of PTB in areas with lower temperatures and higher wind speeds.[36] In

Lanzhou City, China, the incidence of PTB was found to be positively correlated with relative humidity and negatively correlated with wind speed.[37] Li *et al*[38] in a study in eastern China concluded that mean temperature and mean relative humidity were negatively correlated with PTB risk, while mean wind speed was positively associated with it. It can be observed that meteorological factors can have diverse results on PTB depending on the analysing method and the region.

The combined effect of two risk factors provides more explanatory power than any single risk factor when compared with individual variables. Ge *et al*[39] found that the interaction between infrastructure and population density explained the spatial differentiation of PTB prevalence more than individual factors. It has also been shown that environmental factors air pollutants and meteorological factors may show an enhancing effect, for example, temperature and wind speed have a positive effect on PTB incidence by increasing PM.[40] Similar conclusions were reached in our study, especially PM2.5 considering URBMI and public budget income, GDP per capita considering population density and public budget income, and URBMI considering population density. In summary, the effects of each influencing factor on the spread of PTB are not independent but show a mutual or nonlinear enhancing effect.

We also found that the main factors affecting the risk of PTB development in different geographical regions of Xinjiang are different. In the southern region of Xinjiang, population density, GDP per capita and health technicians were the top three factors influencing PTB incidence, whereas in the eastern region, TRSCG, average temperature and public budget revenue had the greatest impact on PTB incidence. In the northern region, GDP per capita, population density and urban health insurance were important determinants of PTB incidence. This heterogeneity may be due to differences in the level of economic development, environmental conditions and geographical features between different geographical areas.[41 42] The causes of this variability among geographical regions require further study in the future.

There are also some limitations in our analysis. Though our study encompassed environmental, public health and socioeconomic variables, many factors with potential influence on PTB incidence, like smoking prevalence, alcohol consumption and personal protective measures, were not included due to the lack of data. Moreover, the study area was in Xinjiang, a high-risk area in China, without further analysis of high-risk areas in other nations. This study is based on a passive monitoring system, and omissions or misses are unavoidable. It is also impossible to avoid the ecological fallacy, which prevents the investigation of individual-based relationships. Hopefully, these limitations will be addressed in future studies.

CONCLUSIONS

In this study, we describe in detail the epidemiological pattern of PTB in Xinjiang, China, identifying the high-risk areas for disease transmission and the influencing factors, as well as the extent to which the interactions among the influencing factors affect the disease. These findings help to suggest targeted intervention strategies for high-risk areas and also help to reduce the disease burden of PTB.

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