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Spatial and temporal clustering analysis of pulmonary tuberculosis and its associated risk factors in southwest China

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Abstract

Pulmonary tuberculosis (PTB) remains a serious public health problem, especially in areas of developing countries. This study aimed to explore the spatial-temporal clusters and associated risk factors of PTB in south-western China. Space-time scan statistics were used to explore the spatial and temporal distribution characteristics of PTB. We collected data on PTB, population, geographic information and possible influencing factors (average temperature, average rainfall, average altitude, planting area of crops and population density) from 11 towns in Mengzi, a prefecture-level city in China, between 1 January 2015 and 31 December 2019. A total of 901 reported PTB cases were collected in the study area and a spatial lag model was conducted to analyse the association between these variables and the PTB incidence. Kulldorff's scan results identified two significant space-time clusters, with the most likely cluster (RR=2.24, p<0.001) mainly located in north-eastern Mengzi involving five towns in the time frame June 2017 - November 2019. A secondary cluster (RR=2.09, p<0.05) was located in southern Mengzi, covering two towns and persisting from July 2017 to December 2019. The results of the spatial lag model showed that average rainfall was associated with PTB incidence. Precautions and protective measures should be strengthened in high-risk areas to avoid spread of the disease.

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Introduction

Tuberculosis (TB) is a chronic communicable disease caused by *Bacillus mycobacterium tuberculosis* (Mtb), which can infect many organs, most commonly the lungs (Bloom *et al.*, 2017). The most important source of infection is an infected person excreting the bacteria. Pulmonary Tuberculosis (PTB) spreads when infected people expel the bacteria into the air, which is common when coughing (Glaziou *et al.*, 2018). Although about a quarter of the world's population is infected with Mtb (WHO, 2020), it does not necessarily directly lead to disease because the pathogen can persist in infected individuals in a latent state for many years. However, when an infected person's resistance is reduced or the cell-mediated allergic reaction increased, disease may arise.

Worldwide, both morbidity and mortality due to PTB are falling. Although the rate of decline has been very slow in recent years, PTB remains the leading cause of death from infectious diseases among adults (Furin *et al.*, 2019). According to the World Health Organization (WHO), an estimated 8.9-11.0 million people fell ill with PTB in 2019 and 1.4 million people died from the disease (WHO, 2020). The top eight countries in WHO's list of 30 high-burden countries accounted for two-thirds of the global total, with China ranking second both with regard to the total number of PTB cases and the global PTB burden (WHO, 2020). In 2019, the morbidity (55.55/100,000) and mortality (0.21/100,000) of PTB ranked second among all notifiable infectious diseases in China (Chinese Ministry of Health, 2019). For decades, considerable efforts have been made to prevent and control PTB. However, without regional specificity and similar control methods, efforts inevitably lead to uneven results, and it is difficult to achieve the goal of PTB control in some areas (Zhang, 2019).

There is a relatively high PTB prevalence in south-western China (Li *et al.*, 2014). The border between Yunnan Province and Myanmar, Laos and Vietnam is characterized by backward economic development, mountainous and a majority of ethnic minorities. The annual notification of PTB was 59.6 per 100,000 population in Yunnan in 2018, while the prevalence was at a moderate epidemic level in the whole country (Chen *et al.*, 2019; Zhao, 2019). The high-incidence areas of PTB in Yunnan Province are mainly in these border areas with poor economic conditions, which is due to the superposition of various factors, such as the social situation, economic conditions and the natural environment (Tang, 2015). In Mengzi, a prefecture-level city located in Southeast Yunnan Province just about 200 km from Vietnam, the reported incidence of PTB has shown a gentle upward trend from 2015 to 2019 (Wang *et al.*, 2022). Studies recommend that the prevention and control of PTB in Yunnan Province should focus on cities with a rising epidemic situation, a high population density and a high proportion of ethnic minorities such as in Mengzi (Qiu *et al.*, 2014).

This study aimed to understand the spatial epidemiological characteristics of PTB in Mengzi in the light of factors related to population and natural conditions. This should provide a theoretical basis for the prevention and control of PTB and achieve the strategic targets of ending the PTB epidemic by 2030 as projected by the United Nations (2015).

Materials and Methods

Study area

Mengzi is the capital of the Honghe Hani and Yi Autonomous Prefecture and the urban core of southern Yunnan. Ethnic minorities account for 55.1% of the total population of 452,000, with the Yi nationality accounting for the largest proportion (26.4%). The city is located in the low-latitude plateau of Yunnan, with little temperature difference throughout the year. The average annual temperature is 18.6 °C. The frequency and intensity of rainfall are high with an average annual rainfall of 813 mm (Li *et al.*, 2021), which is lower than that of Yunnan as a whole (1,089.1 mm) but higher than that of China (630 mm). The town with the highest average annual rainfall is Lengquan (1,290 mm), followed by Laozhai (1,273 mm) and Mingjiu (1,273 mm). The year is divided into a dry season (October to April) and a wet one (May to October; Li *et al.*, 2016). With a total area of 2,228 km^2, the terrain of Mengzi consists of a mountainous area (75.6%) and a one dominated by a dam (24.4%). The city is evenly spread out with a maximum distance of 61 km from East to West and 62 km from North to South. As of 2019, there are 7 towns, 2 townships and 2 ethnic townships in Mengzi (Figure 1).

Data sources

The PTB data in Mengzi was obtained from the System-Infectious Disease Surveillance System, Center for Disease Control and Prevention (China CDC). The population and geographic information were provided by Mengzi CDC. The diagnosis of PTB was based on the official diagnostic criteria for pulmonary tuberculosis covering two separate periods: i) from 1 January 2015 to 9 November 2017 (WS 288-2008) and ii) from 9 November 2017 to 31 December 2019 (WS 288-2017). The study included all new cases of PTB reported from 2015 to 2019 with current addresses in Mengzi.

Statistical models

Kulldorff's spatiotemporal scan statistics (Kulldorff, 1997; Kammerer *et al.*, 2013; Huang, Xu, *et al.*, 2017; Ying *et al.*, 2012) consider both spatial and temporal dimensions of clustering based on a dynamic window covering geographical space combined with various time periods. This is represented by cylinders where the bottom (the window) is the study area and the height the scanning time interval. The radius of the window can be varied to include different sizes of surface (*i.e.* populations to be scanned). The incidence risk is given by the Log-Likelihood Ratio (LLR); the larger the LLR value, the more likely it is to be a cluster area and the window with the largest LLR value is defined as the main cluster. Lower values are defined as secondary clusters. In this study, the maximum window was set at 50% of the population at risk, with time component varied between a minimum of 1 month and a maximum of half the study period.

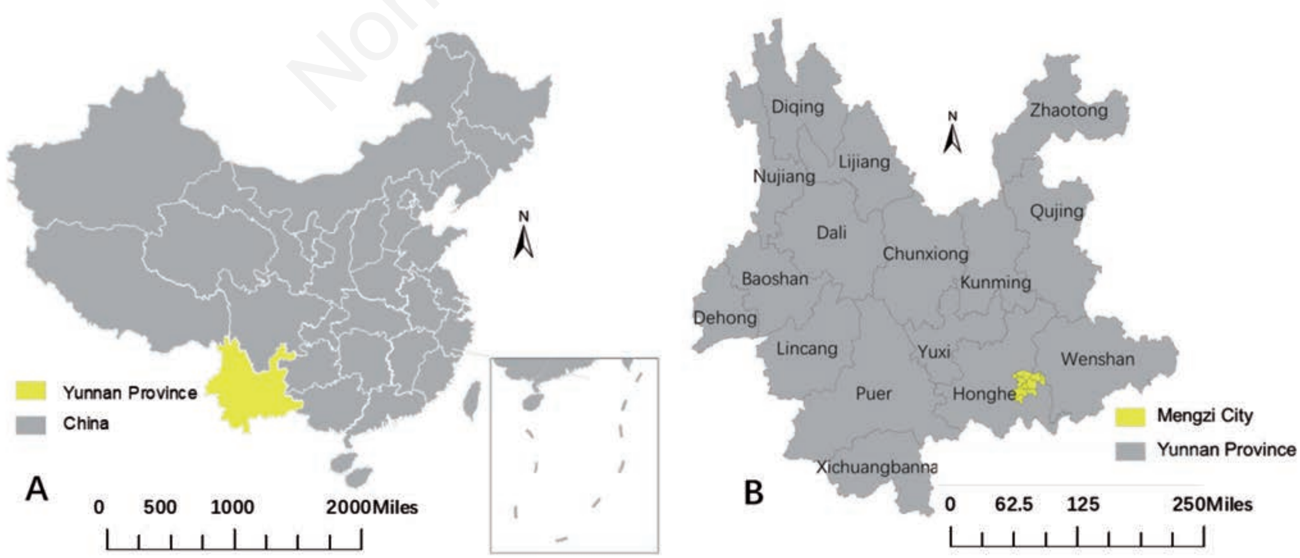

Figure 1. The study area: A) location of Yunnan Province in China; B) location of Mengzi City in Yunnan Province.

Spatial econometrics model analysis (Anselin, 1988; Chen, 2014; Huang *et al.*, 2013; Jiang, 2016) includes spatial dependence and spatial heterogeneity. It is defined as models and theoretical instruments of spatial statistics and spatial data analysis to analyze various economic effects, e.g., externalities, interactions and spatial concentration. Its most important feature is to fully consider the spatial dependence of cross-sectional data, while the premise of spatial metrology analysis is to measure the spatial distance between regions. The spatial data included n regions marked as $\{x_i\}_{i=1}{}^{n}$, where x_i is the region specified by the subscript i. If the distance between area i and area j is w_{ij} the "spatial weight matrix" can be defined as follows:

$$W = \begin{pmatrix} w_{11} & \cdots & w_{1n} \\ \vdots & \ddots & \vdots \\ w_{n1} & \cdots & w_{nn} \end{pmatrix} \qquad \text{Eq. 1}$$

If region i and region j have a common boundary w_{ij}=1, otherwise w_{ij}=0. Where the element w_{11}= … = w_{nn}= 0 on the main diagonal (the distance from the same area is 0).

Existing spatial weight matrix construction methods mainly include spatial distance weight matrices, *e.g.*, a economic spatial weight matrix, a spatial adjacency matrix and a nested weights matrix. However, there is no consensus on the choice of spatial weight matrix at present. We selected the more appropriate spatial adjacency matrix by constructing different weight matrices and used them to compare the results.

There are three main methods of spatial econometrics models in applied research. The Spatial Lag Model (SLM; Anselin, 1988; Chen, 2014) defines that the spatial autocorrelation of variables, which is mainly reflected in the spatial lag term of dependent variables. In our study, it suggests that the reported incidence of PTB in a region is partly affected by the reported incidence of PTB in neighbouring regions. The SLM is expressed as follows:

$$Y=\rho Wy+Bx+\varepsilon \qquad \text{Eq. 2}$$

where Y represents the reported incidence of PTB; ρ the spatial autoregressive coefficient; $W$the spatial weight matrix; W_y the spatial lag-dependent variable; B the parameter matrix to be estimated; $x$the matrix of the $n \times\ k$ explanatory variables; ε the random error term, *i.e.* ε~$N(0, \sigma^2 I_n)$. The spatial autoregressive coefficient ρ reflects the spatial dependence of the sample observations, *i.e.* the direction and degree of the influence of the observations W_y in adjacent regions on the observations y in this region.

The Spatial Error Model (SEM; Anselin, 1988; Chen, 2014) specifies that the spatial autocorrelation of variables is mainly reflected in the error term, indicating that the reported incidence of PTB in a region is affected by the unobserved factors in neighbouring regions. The SEM expression is as follows:

$$Y=Bx+\varepsilon \qquad \text{Eq. 3}$$

$$\varepsilon=\lambda W\varepsilon+\mu$$

where the parameters are the same as before but the parameter μ is the error term and λ the spatial autocorrelation coefficient.

The Spatial Durbin Model (SDM; Anselin, 1988; Chen, 2014) refers to the spatial autocorrelation of variables, which is reflected both in the spatial lag term of dependent variables and in the error term. It shows that the reported incidence of PTB in a region is affected both by the reported incidence of PTB in neighbouring regions and by the explanatory variables in these regions. The SEM expression is as follows:

$$Y=\rho Wy+\theta Wx+Bx+\varepsilon \qquad \text{Eq. 4}$$

where the parameters are the same as before, with the parameter θ as the spatial autocorrelation coefficient of the explanatory variables.

Spatial model selection

Spatial econometric modelling begins with the Ordinary Least Squares (OLS) model, and the residuals of OLS regression were used for the Lagrange Multiplier (LM) test (Chen, 2014). This test contains two statistics: LM-Error and LM-Lag. If these two statistics are not significant, the OLS model should be selected as the final model; if only one of them is significant, the SEM should be selected when it is the former, while the SLM should be selected when it is the latter. If both statistics are significant, the Robust LM test (Chen, 2014; Jiang, 2016) should be used, which also contains two statistics, namely the Robust LM-Error statistic and the Robust LM-Lag statistic. If the former is significant the SEM should be selected, while the SLM should be selected if the latter is significant. If both the LM-Lag and the LM-Error statistics are significant, and the former is greater than the latter, while both the Robust LM-Lag and the Robust LM-Error statistics are not, then the spatial Durbin model should be chosen.

Log likelihood (LL), the Akaike Info Criterion (AIC), the Schwarz Criterion (SC) and R^2 were used to compare the models. The larger the LL and R^2 statistics, the better the model; this is also true, the smaller the AIC and SC statistics. In addition, Wald statistics, Likelihood Ratio (LR) statistics and LM statistics were used to test whether the spatial lag term were significant (the order of these three statistics is suggested to comply with Wald>LR>LM; Jiang, 2016). Autocorrelation was tested by Moran's *I*.

The data were sorted and cleaned using Excel software (version 2016) to create a database of registered cases. The SaTScan™ software (version 10.0) was applied for spatial and temporal clustering analysis. Stata software (version 17.0) was applied for spatial regression analysis. Statistical significance were set at $p<0.05$.

Results

Spatiotemporal clusters

The spatiotemporal scanning results of the incidence of PTB during the 2015–2019 period identified high-occurrence clusters of PTB in the study area. One most likely cluster ($p<0.001$) and one secondary cluster ($p=0.017$) were identified. The most likely cluster had a much higher number of observed cases (182) than expected (91.5). It covered north-eastern Mengzi with coordinates 23.403723N;103.792625E and involved five towns (Laozhai, Mingjiu, Zhicun, Xibeile and Qilubai) within a circle of 34.7 km radius. The cluster period ranged from June 2017 to November 2019 and people living within this cluster had a 2.2 times higher risk of PTB infection than those outside. The LLR was also very high (39.9). The secondary cluster was located in southern Mengzi with coordinates 23.213402N;103.394995E, covered the towns

Lengquan and Shuitian within a circle with a 8.3 km radius and persisted from July 2017 until December 2019. The observed numbers of cases (54) were again much higher than expected (26.7). The residents had a 2.1 times higher risk of PTB during this period compared to those living outside this region. The LLR was 11.2 (Table 1 and Figure 2).

Risk factors

In order to overcome heteroscedasticity, which plagues macrodata, the logarithmic form was used for all variables (independent and the dependent) to make the data stable. A summary of the descriptive statistical results this is provided in Table 2.

The global spatial autocorrelation test performed on the explanatory variable, (reported incidence of PTB) before the regression of the spatial model showed a Moran's *I* value for the reported incidence of PTB of 0.252 with a probability value of 0.024. Thus, the global spatial autocorrelation index rejected the original hypothesis that expected absence of spatial autocorrelation. The local spatial autocorrelation test for 11 towns showed that this original hypothesis could be rejected for some towns, which is consistent with the test results of global spatial autocorrelation.

The results of the OLS regression showed that the five factors had no influence on the reported incidence of PTB. However, if there were a spatial effect, the OLS estimation would be biased.

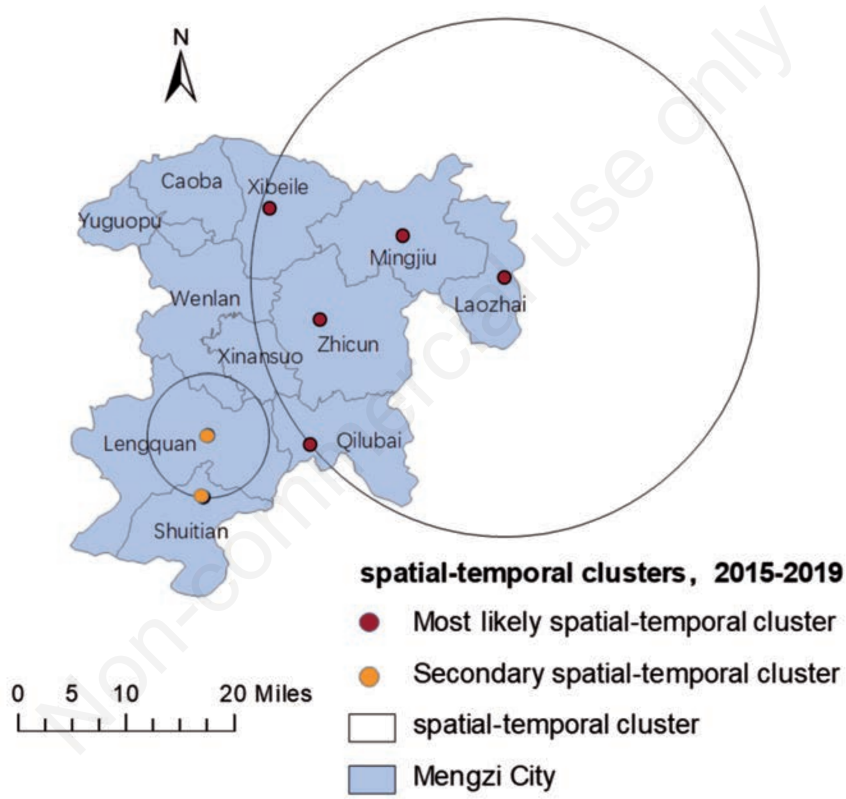

Figure 2. Spatial temporal clusters of pulmonary tuberculosis in Mengzi, China.

Table 1. The most likely clusters of PTB in Mengzi, China 2015–2019.

Cluster Type	No.	District/county	Time frame	Longitude latitude radius	Observed cases	Expected (no.)	RR (no.)	LLR	p-value
Most likely	5	Laozhai, Mingjiu, Zhicunxi Beileqi Lubai	June 2017 to November 2019	23.403723N 103.792625E 34.73 km	182	91.54	2.24	39.87	<0.001
Secondary	2	Lengquan Shuitian	July 2017 to November 2019	23.213402N 103.394995E 8.33km	54	26.71	2.09	11.15	0.017

RR, relative risk; LLR, log-likelihood ratio.

Table 2. Descriptive statistical results of variables.

Variable	Mean	SD	Min	Max
Average temperature	2.82	0.14	2.61	2.99
Average rainfall	6.91	0.21	6.57	7.16
Average altitude	7.37	0.22	7.10	7.65
Crop area	7.53	0.71	6.38	8.99
Population density	4.95	1.02	3.78	6.79
PTB incidence	3.87	0.36	3.28	4.34

N=11; SD, standard deviation.

The residuals of the OLS regression were used for the LM test, the results of which indicated that the original hypothesis expecting absence of spatial autocorrelation should not be rejected in the three tests for spatial error. However, it was rejected in the two tests for spatial lag. Therefore, the study selected the SLM (Table 3). Comparing Tables 3 and 4, it can be seen that both LL (2.6255) and R^2 (0.875) of the SLM were larger than LL (-1.3867) and R^2 (0.742) of the OLS model, while both AIC (10.7489) and SC (13.9321) of the SLM were smaller than AIC (14.7734) and SC (17.1608) of the OLS model. According to the three statistics, the SLM would then indeed be better than the OLS model. The application of Wald, LR and LM statistics to test whether the spatial lag term were significant showed that they completely followed the suggested falling order, that is Wald (11.823, p=0.001) > LR (8.025, p=0.005) > LM (5.590, p=0.018). Thus, all three statistics were statistically significant, which shows that the SLM would be appropriate.

The regression results of the SLM showed that only independent variable, *i.e.* the average rainfall, had a statistically significant and positive impact on the reported incidence of PTB, indicating that the higher the average rainfall, the higher the reported incidence of PTB. The value of the spatial autoregressive coefficient (ρ) was 0.049, *i.e.* it was significant at the level of 0.1%. Therefore, there is the spatial autoregressive effect, which indicates that if the reported incidence of PTB in neighbouring regions increases, the reported incidence of PTB in the core regions would also increase (Table 4).

Table 3. Lagrange multiplier test results.

Variable	Coefficient	SE	T value	p-value
Constant	-29.659	21.129	-1.40	0.219
Average temperature	2.210	3.083	0.72	0.505
Average rainfall	1.668	1.725	1.49	0.196
Average altitude	2.176	1.725	1.26	0.263
Planting area of crops	0.029	0.292	0.10	0.925
Population density	-0.092	0.323	-0.28	0.788
R^2	0.742	-	-	-
Log likelihood	-1.3867	-	-	-
Akaike info criterion	14.7734	-	-	-
Schwarz criterion	17.1608	-	-	-
Spatial error				
Moran's *I*	1.394			0.163
Lagrange multiplier	0.004			0.947
Robust Lagrange multiplier	0.228			0.633
Spatial lag				
Lagrange multiplier	5.590			0.018
Robust Lagrange multiplier	5.814			0.016

SE, standard error.

Discussion

In 2004, China established a legal, real-time report information platform of infectious diseases covering the whole country. The monitoring of this kind of data reflects the presence and spread of diseases to a certain extent, which plays an indispensable role in the prevention of infectious diseases. PTB is classified into Class B, which requires new PTB patients to be reported within 12 hours in urban areas and 24 hours in rural areas. Therefore, the data in this paper are close to the true, current level of the PTB epidemic in Mengzi.

Our study shows that the incidence of PTB has a strongly spatial-temporal clustering in Mengzi, which is consistent with previous findings by Huang, Li *et al.* (2017), Huang *et al.* (2018), Chen *et al.* (2019) and ourselves (Wang *et al.*, 2022). In summary, these papers show that PTB is concentrated along the south-western and north-eastern border areas of Yunnan Province. Our earlier study used local spatial autocorrelation to find hotspots and coldspots of PTB in Mengzi and it is worth mentioning that we also found an

Table 4. Spatial lag model results.

Variable	Coefficient	SE	Z value	p-value
Constant	-13.935	10.894	-1.28	0.201
Average temperature	0.504	1.525	0.33	0.741
Average rainfall	1.693	0.523	3.23	0.001
Average altitude	0.836	0.897	0.93	0.351
Planting area of crops	-0.257	0.160	-1.61	0.108
Population density	-0.031	0.152	-0.21	0.837
Rho	0.049	0.014	3.44	0.001
R^2	0.875	-	-	-
Log likelihood	2.6255	-	-	-
Akaike info criterion	10.7489	-	-	-
Schwarz criterion	13.9321	-	-	-

SE, standard error; Rho, autoregressive coefficient.

additional, secondary cluster area in southern Mengzi through spatial-temporal scanning (Wang *et al*., 2022). Tadesse *et al.* (2018) argue that since there is no gold standard to detect disease clusters spatiotemporally, it is preferable to use more than one method to cross-validate the results.

Differences in socioeconomic level, geographical and climatic conditions among the various regions are the main reasons affecting the susceptibility and control of PTB (Zhang, 2019). Laozhai and Qilubai, two of the autonomous towns located in the most likely cluster area, are mainly inhabited by the Miao Minority. There are also people belonging to the Yi Minority in this area and most of these minorities are farmers. As there is a higher rate of PTB cases in the cluster area than elsewhere, it seems that there is an association between PTB infections and the ethnic minorities, who often have a lower socio-economic status than the rest of the population (Li *et al.*, 2013; Liu *et al.*, 2018; Wubuli *et al.*, 2015).

Under the dual influence of altitude and the southwest monsoon in the Bay of Bengal, the southern region of Yunnan has abundant precipitation, thus forming a rainy region (Liu *et al.*, 2020). We found that the average rainfall was positively correlated with the reported incidence of PTB, which is consistent with several authors (Li *et al*., 2014; Li *et al.*, 2019; Zhang *et al.*, 2019). Activation of latent PTB by increased air humidity (which is an effect of rain), as suggested by Xiao *et al.* (2018), is one possible explanation.

PTB is felt to be positively related to the population density (Sun *et al.*, 2022), while Selmane *et al.* (2021) argue that the general population density cannot be considered but that it is rather overcrowded areas, such as poor areas in certain cities that contribute to the spread of PTB. Some studies indicate that altitude is positively associated with the incidence of PTB because high oxygen tension is greatly beneficial with regard to the proliferation of Mtb *in vitro* (Sun *et al.*, 2015; Tanrikulu *et al.*, 2008; Vargas *et al.*, 2004). In addition, ultraviolet exposure is higher at higher altitudes, leading to higher levels of Vitamin D that may decrease the risk of active PTB (Gelaw *et al*., 2019; Noaham & Clarke, 2008). A study conducted in Jinghong, Yunnan Province in 2006-2015 reports that the average temperature is negatively correlated with PTB incidence, possibly due to the fact that temperature directly changes the timing of indoor/outdoor activities of both PTB susceptible and infected populations and thus influences transmission (Xiao *et al.*, 2018). Other studies have also shown that the prevalence of PTB is higher in areas where the temperature is high, possibly because higher temperature helps to promote the activity of bacteria and improve their viability (Cao *et al.*, 2016; Li *et al.*, 2014). However, our study did not draw the above conclusions, a difference of results that may be due to the small size of the study area and the small differences effected by factors, such as altitude and temperature between regions, so further studies are needed.

Ecological studies cannot provide conclusive results but can generate and develop hypotheses (Zhang *et al.*, 2019). Variations in PTB incidence associated with rainfall, altitude and temperature have been widely assumed (Cao *et al.*, 2016; Li *et al*., 2019; Sun *et al.*, 2015; Tanrikulu *et al.*, 2008; Vargas *et al.*, 2004). The influence of these factors has not been well studied, and the inconsistent results may be due to statistical models of different studies and regional differences. Meteorological factors may have a noticeable effect on future PTB incidence (Xiao *et al.*, 2018) and if patterns can be grasped and informed prevention and preparedness measures for PTB developed based on meteorological variations, it might be possible to effectively reduce the PTB incidence.

This is the first study applying spatiotemporal scanning analyzing the influencing factors of PTB at the town level in Mengzi, China, which may be the best first step for PTB control. However, several limitations were encountered: i) since the areas showing clustering are likely to be irregularly shaped, Kulldroff's cylindrical window might have included areas not belonging to the cluster(s); ii) all factors possibly associated with the PTB clustering were not included in this study because of lack of monitoring data; iii) we could only show the correlation rather than causality between average rainfall and the reported incidence of PTB; iv) spatial data of diseases often have spatial heterogeneity, which is not considered by SLM. The parameter estimates in this model are global average estimates, which assume that the impact of such indicators as annual rainfall on the incidence of PTB is the same among different study areas. The presence of these limitations boils down to a strong need for further research in the future.

Conclusions

A strong spatial-temporal clustering effect existed in the reported incidence of PTB in Mengzi during 2017-2019. Our results showed that PTB clusters were mainly concentrated in the Northeast and South and that average rainfall is an important factor for spatial clustering of PTB. Prevention and control intervention should target these clusters.

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