Abstract of the Dissertation submitted by Lu Yixiao

Title: Spatial-temporal analysis of tuberculosis infections in a rural prefecture in Japan

Japanese title: 日本の地方県における結核感染の時空間分析

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ACTA MEDICA NAGASAKIENSIA, in press
〔Total page number :24〕

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Introduction

Tuberculosis (TB) is a bacteria-caused infectious disease which generally results in pulmonary TB as well as extrapulmonary TB; and TB is one of the top 10 causes of death worldwide. Japan has remained a medium-burden TB country for many years. The Ministry of Health, Labour and Welfare of Japan (MHLW) announced the "Stop TB Japan Action Plan" in 2008 and initiated the "Stop TB Japan" in 2015 to fight TB. The TB notification rates have significantly decreased since 1980; however, the incidence of TB increased among the older population, the younger population, and the foreign-born population from high-burden TB countries was observed. Moreover, a considerable variation was observed in the TB space-time distribution among Japan's eight regions.

Studies evaluating the spatial and temporal distribution of TB have reported the highly complex dynamics and spatially heterogeneous distribution (national and provincial) of TB infection in different periods. However, the variation in small regions are often neglected in such large-scale analysis. Besides, a better understanding of the spatial epidemiology of TB could help policymakers to formulate effective prevention and control strategies.

Therefore, this study aimed to investigate the spatial, temporal, and space-time dynamics of TB at a fine scale (*machi*-level) in Nagasaki prefecture.

Materials and Methods

Study setting and data sources

This study was set in Nagasaki prefecture where in total 1,943 *machi*s are registered according to the 2015 national census data. The total population in 2018 was 1.3 million. Data on the reported TB infections were extracted from the information center for infectious diseases of the Nagasaki Prefectural Institute of Environment and Public Health.

Statistical analysis

The global Moran's I was used to measure whether the reported TB infections from *machi* in Nagasaki prefecture is affected by the neighboring regions. The Kulldorff's space-time scan statistic method was used to detect the temporal, spatial, and space-time clusters of TB infections. The potential clusters are the areas with high TB notification rates that had significantly exceeded the TB notification rates of nearby regions ($p < 0.05$). The potential cluster with the maximum likelihood ratio (*LLR*) was defined as the most likely cluster, while the rest of clusters with statistically significant *LLR* were defined as the

secondary clusters ($p < 0.05$). Additionally, the time-series analysis based on the additive decomposition model was used to estimate the seasonal effects on the reported TB infections in Nagasaki prefecture from 2007 to 2018.

Results

A total of 4,364 TB infections were reported from April 2007 to December 2018. 1206/1943 *machi*s in Nagasaki prefecture have reported at least one case of TB infection.

The time-series of TB infections indicated slightly upward and downward trends between 2007 and 2013, followed by a sudden increase until early 2014, a decrease in mid-2014 and mid-2015, and a slowly increasing trend after 2015. TB infection had no apparent periodicity seasonality and seasonal effects between 2007 and 2018. The maximum seasonal index values were 1.15 in October, 1.14 in June, and 0.83 (the lowest value) in January. The high aggregated period for TB was from February 20, to March 19, 2014, with 84 reported TB cases ($LLR = 36.9$, $p = 0.001$).

The annual global Moran's I value indicated a positive spatial autocorrelation in Nagasaki prefecture, ranging from 0.07 to 0.17 ($p = 0.001$). The spatial clustering analysis identified five significant spatial clusters, covering 215 *machi*s. The most likely cluster was identified in T-*machi* in Nagasaki city ($LLR = 59.72$, $p < 0.001$); the secondary clusters were identified near Nagasaki port and Sasebo port, in the Shimabara peninsula, and in A-*machi* in remote Goto island.

The retrospective space-time scan statistics identified ten significant clusters. The most likely cluster was identified in T-*machi* in Nagasaki city, with 34 reported TB cases, and the high-risk period was from September 1 to December 31, 2007 ($LLR = 167.81$, $p < 0.001$). The secondary clusters were identified in Nagasaki city, Sasebo city, Shimabara peninsula, Goto island, and Iki island. The cluster with the most extended duration (secondary cluster 3) was detected in Shimabara peninsula, including almost the entire Unzen city and a part of Minamishimabara city.

Discussion

This study was the first to investigate the status of TB infections at the *machi*-level in a rural prefecture with relatively high TB notification rate in Japan. Our study demonstrated a significant space-time clustering in the distribution of TB infections in Nagasaki prefecture. The high-risk areas were mainly concentrated in the densely inhabited districts (DIDs) of the two biggest cities in Nagasaki prefecture (Nagasaki city and Sasebo city), Shimabara peninsula, and Iki island. Temporal clustering was sporadic in the autumn, winter, and early spring, that is, from September to mid-March.

Of the 4,364 notified TB infections between April 2007 and December 2018 in Nagasaki prefecture, the majorities were older than 65 years, and the notification rate was extremely high in men aged > 85 years. In Japan, TB is primarily detected during regular health checkups among schoolchildren and workers; however, the fixed timing of annual health checkups could cause problems like delays in healthcare seeking and non-detection of TB cases during regular screening. Therefore, provision of geographical information on TB infections on a small scale could help adopt appropriate measures for the early diagnosis of TB among the high-risk populations.

This study analyzed the spatial, temporal, and space-time clusters of TB infection at the *machi*-level in Nagasaki prefecture from April 2007 to December 2018. Results showed significant and unique spatial-temporal characteristics of TB infection the region.
(906 words)