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Spatial and Temporal Disparities of Leptospirosis Transmission in Sarawak (Malaysia), 2011-2018

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ABSTRACT

This study is to analyse the spatial distribution of leptospirosis and identify its high and low incidence clusters in Sarawak. The annual incidence rate at the district level was calculated using confirmed report of leptospirosis cases from year 2011 to 2018. Empirical Bayes estimation smoothing of relative risks was used to display the spatial distribution of leptospirosis across the study region. Moran's Global Index and Local Indicators of Spatial Association (LISA) were used to analyse the existence of global and local spatial autocorrelation. Data were analysed using ArcGIS and Geoda software at the district level. The annualised average incidence reported during the study period was 20.83 per 100,000 population, with the highest cases reported in year 2018 (n = 870). The Global Moran's Index revealed spatial clustering of leptospirosis incidence in 2012 (Moran's *I*: 0.23), 2013 (Moran's *I*: 0.33), and 2014 (Moran's *I*: 0.45), while 2011 (Moran's *I*: -0.01), 2015 and 2016 (Moran's *I*: 0.09), 2017 (Moran's *I*: 0.13), and 2018 (Moran's *I*: 0.04) showed random patterns. High incidence clusters of leptospirosis were primarily congested in the Southeast of Sarawak, involving districts such as Kapit, Belaga, Song, Tatau and Lubok Antu. Spatial and temporal patterns of leptospirosis incidence were heterogeneous across Sarawak. This study facilitates the implementation of targeted interventions and control measures for leptospirosis in Sarawak by identifying spatial cluster and outliers.

Keywords: Leptospirosis, Local Indicator of Spatial Association (LISA), Moran's Global Index, Sarawak, spatial analysis

INTRODUCTION

The global burden of leptospirosis is estimated at 0.10 – 975 cases per 100,000 populations and with a fatality rate of 6.85% depending on the population's prevalent serovars, healthcare services, and economic status (WHO, 2015). The disease is caused by a *Leptospira* sp. that colonises the kidneys of a wide diversity of peri domestic animals such as rats, horses, cows, dogs, and pigs and wild animals such as bats, coyotes, and sea lions (Barragan *et al.*, 2017). Human infections occurred through the exposure of abraded skin and mucous membrane to leptospiral-contaminated environments and direct transmission. Symptoms for leptospirosis include a mild influenza-like illness, Weil's syndrome characterized by jaundice, renal failure, haemorrhage and myocarditis with arrhythmias meningitis, pulmonary treatment haemorrhage with respiratory failure. Early with antibiotics such as penicillin, doxycycline, tetracycline, ampicillin or amoxicillin is essential (Disease Control Division, 2011). The burden of human leptospirosis was prevailing in the tropical and subtropical regions, with a prominently high incidence in Southeast Asia such as India, Bangladesh, Nepal, Thailand, Sri Lanka and Indonesia (Bahaman & Ibrahim, 1988; Kawaguchi *et al.*, 2008; Benacer *et al.*, 2016; Hinjoy, 2016). In addition, factors including poor environmental hygiene, the proliferation of reservoir hosts, socio-economic status, contact with infected animals, and recreational activities have compounded the predisposition of humans and susceptible animals to the risk of contracting leptospirosis (Garba *et al.*, 2018).

In Malaysia, leptospirosis is endemic and gazetted as a notifiable disease since December 2010 under the Prevention and Control of Infectious Diseases Act 1988 (Disease Control Division, 2011). Statistic for leptospirosis cases in Malaysia for the 2-year survey period showed that, the overall case incidence rate for leptospirosis was 29.02 per 100,00 population, and the overall case fatality rate for leptospirosis was 1.47% on year 2012 and 2013 (Tan *et al.* 2016).

This infection highlights a necessity in identifying priority areas to facilitate surveillance programs and interventions for control. In recent years, the development of Geographical Information Systems (GIS) has provided a robust and rapid ability to examine spatial and temporal patterns and processes by incorporating metadata into its analysis. In turn, it has fostered the utilisation of spatial and temporal statistics for environmental investigations of infectious diseases (Moore & Carpenter, 1999). Previous studies have adopted GIS analysis tools in the study of ecological models to explore and analyse spatial variations in relationships between local environmental factors and the occurrences of leptospirosis (Trueba *et al.*, 2004; Vega-Corredor & Opadeyi, 2014; Widayani *et al.*, 2016; Mohammadinia *et al.*, 2017; Mayfield *et al.*, 2018).

In the present study, spatial statistics was applied to study the spatiotemporal distribution of confirmed leptospirosis cases reported in Sarawak from 2011 to 2018. Therefore, the objectives of this study were to visualise the geographical trend of leptospirosis incidence over the eight years' study period from 2011 to 2018 and to determine if leptospirosis in Sarawak demonstrates global and local spatial clustering. For this study, it was hypothesised that there would be significant difference in spatial clustering in leptospirosis incidence rate among the districts in Sarawak.

MATERIALS AND METHODS

Study Area

The state of Sarawak is located between 1.5533º N and 110.3592º E on the island of Borneo (Figure 1). Sarawak is the largest state in Malaysia with a total area of 124,450 km^2. According to the 2014 census report, Sarawak has 2,738,700 inhabitants, with a population density of 22 people per km^2 (Department of Statistics Malaysia, 2019). The population is congested in the western regions such as Kuching (451 people per km^2). In comparison to the western regions, the southeast area of Sarawak, such as Kapit, is the most sparsely populated with 16 people per km^2 (Department of Statistics Malaysia, 2019). Based on the official administrative classification, there are 12 divisions with 30 districts in Sarawak. The district boundary map used in the study was obtained from the Database of Global Administrative Areas, GADM (Areas, 2012). Sarawak has an equatorial climate and experiences two monsoon seasons: northeast monsoon (rainy season) and southwest monsoon (dry season). The average minimum and maximum temperatures are 23.8 ℃ and 32.1 ℃, respectively with a mean humidity of 84.4%. On average, the amount of rainfall in Sarawak is approximately 3,696.29 mm (Department of Statistics Malaysia, 2019).

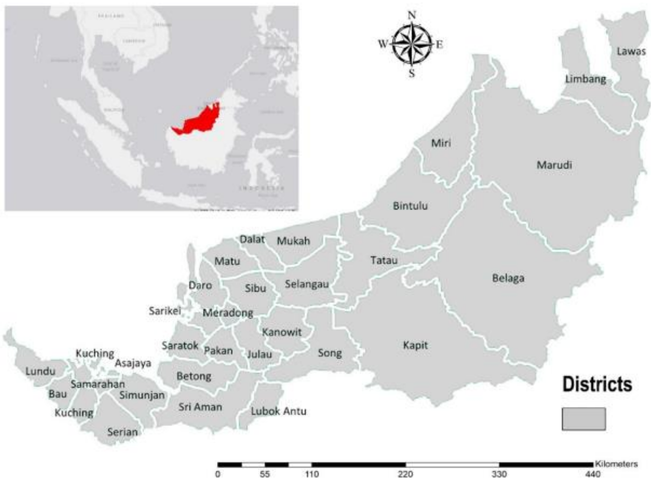

Figure 1. Map showing the 30 districts in the state of Sarawak, Malaysia

Data Collection and Management

Ethical approval for the study was obtained from the National Medical Research (NMRR, Ethical Number:18-2713-42365), Ministry of Health Malaysia (MOH). Reported leptospirosis cases in Sarawak from years 2011 to 2018 were retrieved from the Infectious Disease Unit, Sarawak State Health Department. All data obtained were anonymous to ensure confidentiality. Cases were confirmed through clinical evaluation and laboratory diagnostic tests. Under the guideline published in 2011, confirmed cases of leptospirosis must be notified within one week to the district health office. A probable case of leptospirosis is defined as a subject with positive ELISA or any other rapid tests. A confirmed leptospirosis case is defined as a suspected or probable case with confirmatory microscopic agglutination test (MAT) with single serum specimen - titre ≥1:400 and for paired sera of four-fold or higher rise in titre (Disease Control Division, 2011). The dataset comprises the number of confirmed cases in each district.

Spatiotemporal Incidence Mapping

Leptospirosis cases were aggregated according to districts (analytical units). The annual incidence (A.I.) rate per 100,000 population for each district was calculated by dividing the number of cases each year by the corresponding district population obtained from the Department of Statistics Malaysia (Department of Statistics Malaysia, 2019). The average incidence (AveI) of leptospirosis in Sarawak in each district over the eight years was also included in spatial data analysis. A contiguity spatial weight matrix for each analytical unit level was created based on first-order neighbourhood criteria. For this study, the neighbours were defined as areas with shared borders and vertices (queen). Spatial smoothing was applied to reduce random variation in the incidence rate associated with small population size (Anselin *et al.*, 2006). According to Cardoso *et al.* (2019), the incidence rates for each analytical unit were re-estimated using the Spatial Empirical Bayesian smoothing approach executed in GeoDa software version 1.6.7 (ASU, GeoDa Center for Geospatial Analysis and Computation, Arizona, USA).

Spatial Autocorrelation Analysis

Global Moran's *I* spatial auto correlation statistics were calculated to check whether the A.I. demonstrates a spatial dependence pattern. Annual Incidence from 2011 to 2018 in each analytical unit and the Ave I were included in the analysis. The annual incidence rate for each district was standardised similarly as a statistical z-score that compares observations to the mean to determine the observations' relative position within a distribution. The continuous Moran's Global index value can vary from -1, indicating an inverse correlation (dispersed) to +1, showing a direct correlation (clustered). Values of zero or close to zero suggest a random distribution (Moran, 1948; Cardoso *et al.*, 2019).

Spatial Cluster Analysis

Univariate Local Indicators of Spatial Association (LISA) were computed to identify local clusters in each year. LISA analysis divides the value of Moran's Global Index, reflecting the value of each unit of analysis, and indicates whether there are associations with neighbours and the presence or absence of outliers (Anselin, 1995). The four quadrants generated by LISA analysis represent four types of local spatial autocorrelations: Quadrant I (high-high type, or H.H.: indicates high A.I. values surrounded by high A.I. values); quadrant II (high-low type, or H.L.: indicates high A.I. values surrounded by low A.I. values); quadrant III (low-high type, or L.H.) indicates low A.I. values surrounded by high A.I. values); and quadrant IV (low-low type, or L.L.: shows low A.I. values surrounded by low A.I. values) (Anselin, 1995). The number of permutation test was set to 999, and the significance level was set as 0.001. Analyses of Moran's Global Index and LISA were performed using GeoDa Software version 1.6.7, and maps were constructed using the ArcGIS 10.3 software (Environmental Systems Research Institute, California).

RESULTS

Spatiotemporal Incidence Mapping

A total of 4,642 leptospirosis cases were reported in Sarawak with annualised average incidence (AveI) of 20.83 per 100,000 population during the of eight years' study period. However, the A.I. oscillated between 2.17 and 31.19 per 100,000 population. Comparison of leptospirosis cases by years revealed the highest in 2018 (n = 870) and lowest in 2012 (n = 61) (Figure 2).

The highest incidence rate across the study region was reported in Kapit district with an average of 86.28 per 100,000 populations. Leptospirosis cases reported in the Kapit district ranged between 7 and 132 cases, with an average of 57 cases per year. Pakan district reported the lowest incidence rate in Sarawak with 7.79 per 100,000 population. The number of cases in Pakan alternates between zero and eight cases during the eight years' study period. Higher incidence rates were concentrated in the southeast region of Sarawak, involving districts such as Kapit, Belaga, Song, Tatau, Kanowit and Lubok Antu. These districts reported smoothing average incidence rates were higher than 29.70 per 100,000 inhabitants (Figure 3).

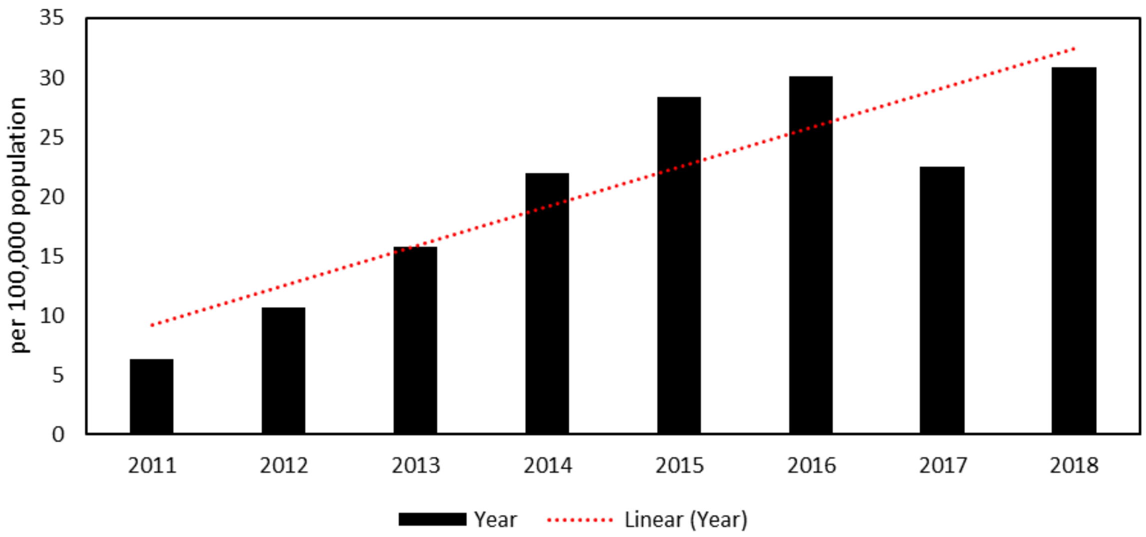

Figure 2. Annual incidence rate of leptospirosis in Sarawak from 2011 to 2018. The dotted red line represents the trend of leptospirosis over the study period

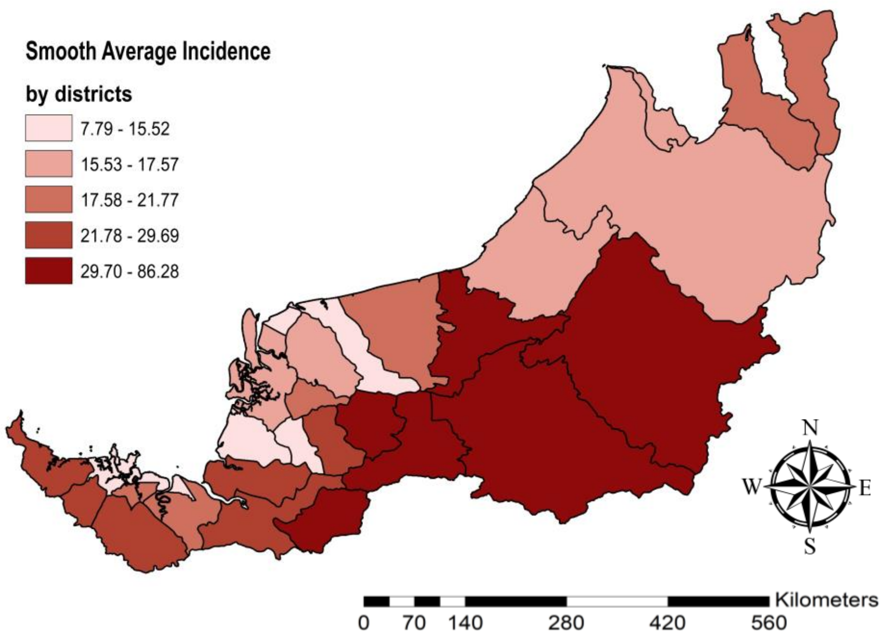

Figure 3. Spatially smoothed maps of annualised average incidence per 100,000 population using spatial empirical Bayesian smoothing

Global Spatial Autocorrelation

The Moran's Global Index for the annual incidence rate revealed a variation in the spatial distribution of leptospirosis cases reported from 2011 to 2018 (Table 1). Overall, the leptospirosis incidence rate in Sarawak demonstrated a positive spatial clustering (Moran's *I*: 0.28). Significant positive clustering was observed in year 2012 (Moran's *I*: 0.23) and 2013 (Moran's *I*: 0.33), with the highest Moran's Global Index in year 2014 (Moran's *I*: 0.45). Random spatial patterns were reported in year 2011, 2015, 2016, 2017, and 2018 (p>0.05) (Table 1).

Table 1. Summary of global Moran's *I* analysis for leptospirosis incidence in Sarawak

Period	Moran's Index	Z	p-value	Pattern
2011	-0.01	0.33	0.30	Random
2012	0.23	2.10	<0.05	Clustered
2013	0.33	2.61	<0.05	Clustered
2014	0.45	3.60	<0.05	Clustered
2015	0.09	1.38	0.10	Random
2016	0.09	1.15	0.13	Random
2017	0.13	1.19	0.12	Random
2018	0.04	0.68	0.23	Random
AAI	0.28	2.97	<0.05	Clustered

*AAI: Annualised incidence rate

Local Clusters and Outliers

The annual incidence rates of leptospirosis cases were heterogeneous across all 30 districts during the eight years' study period (Figure 4). High-high (H.H.) cluster was not reported in year 2011, but significant low-low (L.L.) clusters were noticeable in the western districts involving Matu, Daro and Dalat districts. Song district was identified as a significant high incidence cluster (H.H.) starting from year 2015 to 2018. On the other hand, the Sarikei district was revealed as a significantly low cluster (L.L.) from year 2014 to 2018. Interestingly, more districts showed significant clustering in year 2014, with four districts identified as H.H. clusters and eight districts as L.L. clusters. Besides high and low clusters, spatial outliers of high (H.L.) and low (L.H.) incidence rate were also observed in this study. Outliers of high incidence rate (H.L.) of leptospirosis incidence was reported in year 2015 and 2016, which involved Betong and Kota Samarahan districts. Tatau district was a significantly low incidence outlier in 2012 and 2017, while in 2013, Kapit was the significant outlier. Overall, H.H. clusters are predominantly localised in the southeast districts, while clusters of low incidence rate (L.L.) were identified in the western region involving districts such as Matu and Sarikei. The total number of significant spatial clusters by years are summarised in Table 2.

Table 2. Number of spatial clusters identified based on LISA analysis

Year	Spatial Pattern				
	H.H.	L.L.	H.L.	L.H.	Not Significant
2011	0	3	0	0	27
2012	1	5	0	1	23
2013	2	3	0	1	24
2014	4	8	0	0	18
2015	1	1	2	0	26
2016	1	1	1	0	27
2017	1	2	0	1	26
2018	1	2	0	0	27

* H.H.: High-high type; L.L.: Low-low type; H.L.: High-low type; L.H.: Low-high type

DISCUSSION

The research question investigated in this study is whether prevalence of leptospirosis infections in Sarawak demonstrates the spatial-temporal pattern during the study period. From the result in this study, it has proved that the leptospirosis demonstrated significant spatial and temporal patterning. The heterogeneity in spatial clusters and the emergence of outliers (HL/LH) may be linked to the changes in local risk factors such as demographical, ecological and socioeconomic characteristics during the study period (Dhewantara *et al.,* 2018). Behavioural risk factors of the local population could potentially promote disparities in the spatiotemporal distribution of leptospirosis cases in the current study (Goarant, 2016). For instance, the utilising of jungle resources for food and supplementary income will result in frequent trips to the jungle, and involved in water-based recreational activities also increases regular contact with water bodies such as lakes or rivers. These circumstances facilitate pathogenic *Leptospira* sp. from the environment and elevate the risk of infection among susceptible hosts. A higher risk

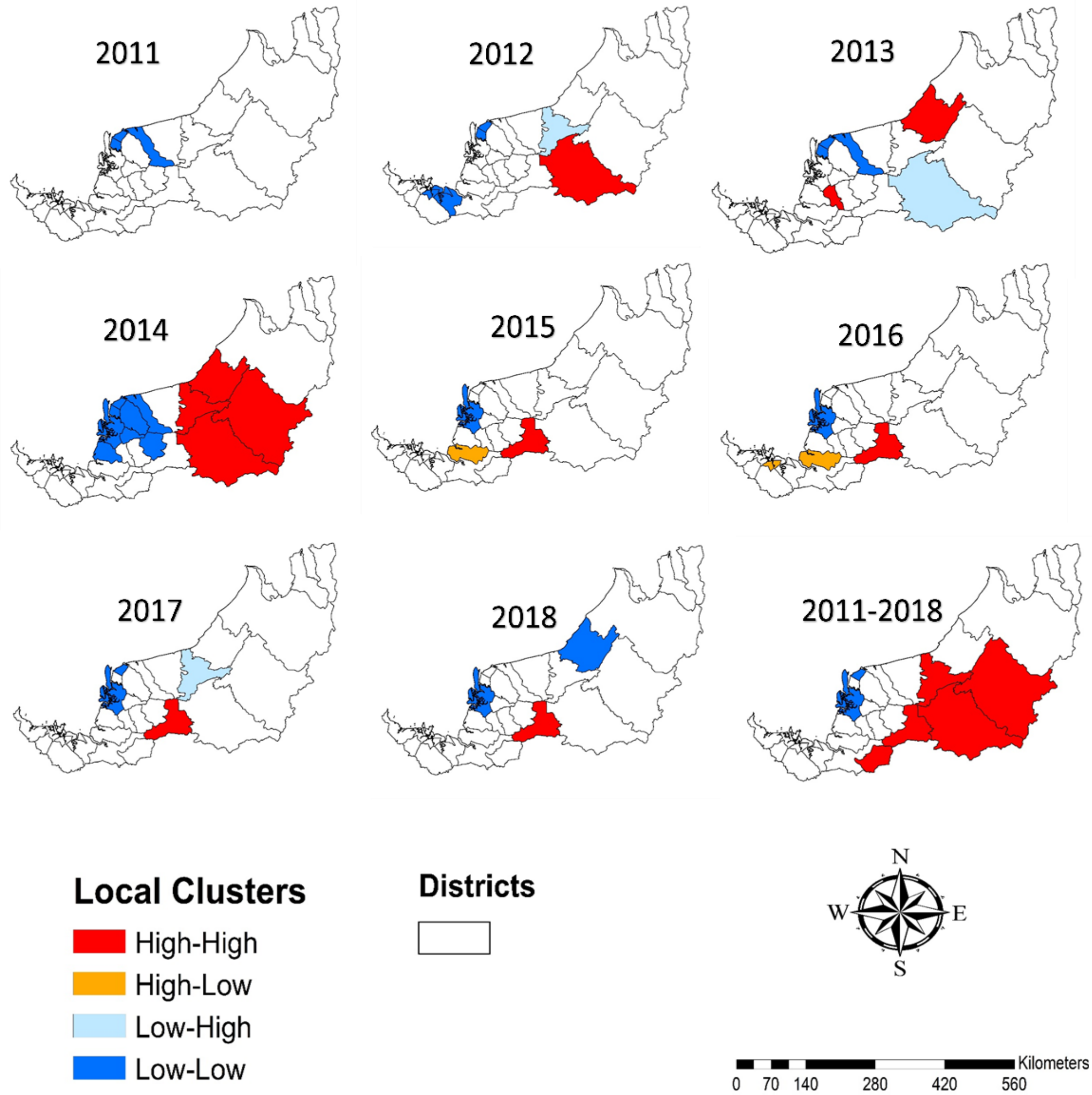

Figure 4. High and low leptospirosis incidence clusters and outliers identified based on LISA analysis. Colour-coded polygons indicated districts with significant spatial clustering, while the blank polygons indicated areas with insignificant spatial clustering. The figure shows the LISA map by years, from 2011 to 2018

of *Leptospira* infection has been shown in communities with frequent contact with lakes or rivers (Philip *et al.*, 2013). Leptospirosis outbreaks have been reported following exposure to contaminated water and soil during sporting activities like jungle hiking, water rafting and swimming in Sabah, Malaysia from 21 August to 1 September 2000 (Haake *et al.*, 2002; Sejvar *et al.*, 2003; Wynwood *et al.*, 2014). In addition, the zoonotic importance of mammalian species such as monkeys, bats, and rats in carrying leptospirosis in Sarawak have also been documented in previous literatures (Thayaparan *et al.*, 2013; Pui *et al.*, 2015; Suut *et al.*, 2018). Pathogenic Leptospiral were proven to circulate in multiple environmental and ecological settings like national parks, paddy fields and national service centres in Sarawak (Pui *et al.*, 2015; 2017a; 2017b). Such information evokes the possibility for a shift in the transmission paradigm of leptospirosis, which could explain the spatiotemporal disparities of this disease in Sarawak.

The occurrences of high (H.H.) and low (L.L.) incidence clusters may be linked to the existence of local characteristics that are commonly shared by the clustered region. For instance, socioeconomic factor such as occupational types could discriminate the predisposition of the susceptible population in different districts (Mohd Radi *et al.*, 2018). The significance of occupational exposures as an essential risk factor for leptospirosis has been documented in previous studies (Chou *et al.*, 2008; Goris *et al.*, 2013; Benacer *et al.*, 2016; Tan *et al*., 2016). A study in China reported that counties with a higher risk of leptospirosis predominantly observed on younger population, more males and farmers, compared to the low-risk counties (Dhewantara *et al.,* 2019). High-risk counties were also economically less developed and more rural with higher precipitation of population (Dhewantara *et al.*, 2019). In the present study, the south-eastern region of Sarawak is at the highest risk increasing leptospirosis cases. This finding is supported by Su'ut *et al.* (2016), where the rapid development in the Rejang Basin through dam construction, the opening of the vast plantation, rural environment, and other subsistence activities performed by the local communities could have facilitated interaction between humans and rodents' host leptospiral-contaminated environment hence resulting to high seroprevalence (Su'ut *et al.*, 2018).

Leptospira spp. have also been proven to circulate among domestic and wildlife animals including dogs, cattle, primates, rats and bats (Bahaman *et al.*, 1988; Thayaparan *et al*., 2013). The presence of garbage and other wastes fosters due to human activities cause the proliferation of reservoir animals such as rats. Such circumstances highlight the relevance of animal contacts and host abundance as risk factors contributing to the transmission of leptospirosis in rural areas.

Furthermore, the high annual rainfall in the Rejang Basin coupled with seasonal flooding during monsoon season contributed to the high seroprevalence in these areas (Suut *et al.*, 2016). A similar observation was reported in Kelantan, where clusters of high leptospirosis incidence were observed during the post-flood period (Mohd Radi *et al.*, 2018). According to Jones *et al.* (2013), the encroachment of human settlements and agriculture on natural ecosystems has led to the expansion of ecotones (transition zones between adjacent ecological systems), where species assemblages from different habitats mix. This provides new opportunities for pathogen spill over, genetic diversification, and adaptation (Jones *et al.*, 2013). Associations between disease emergence and ecotones have been suggested for several diseases, including leptospirosis (Jones *et al.*, 2013).

A further study is suggested to model the relationship in other districts to provide a more comprehensive understanding of the influence of environmental variables on the distribution of leptospirosis cases in Sarawak. As the current studies, leptospirosis cases were aggregated by districts that prohibit analysis at a higher spatial resolution, and significant clusters might be filtered out. However, this is the highest resolution at which the data are currently available. Additionally, the analysis here focused on the geographic distribution of leptospirosis transmission without examining the causes of its transmission. Future research should identify critical factors (socio-economic, demographic, environmental) and incorporate multivariate analysis to comprehend the transmission dynamics of leptospirosis cases reported in Sarawak.

CONCLUSION

In conclusion, this study has revealed that the transmission of leptospirosis was heterogeneous across Sarawak, and spatial clustering appeared to vary over the eight years' study period starting from 2011 to 2018. To the best of our knowledge, this is the first study to examine the spatial variation of leptospirosis transmission in Sarawak, Malaysia using GIS analysis approaches and lays a foundation for further investigation into social and environmental factors responsible for changing disease patterns. Furthermore, results obtained in this study can identify high-risk areas where priority should be given in terms of surveillance and public health interventions.

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