Faculty of Resource Science and Technology

Assessment of Environmental Variables as Potential Risk Factors for the Transmission of *Leptospira* spp.

Rosdi Anak Kira

Master of Science
2020

Assessment of Environmental Variables as Potential Risk Factors for the Transmission of *Leptospira* spp.

Rosdi Anak Kira

A thesis submitted

In fulfillment of the requirements for the degree of Master of Science

(Environmental Microbiology)

Faculty of Resource Science and Technology
UNIVERSITI MALAYSIA SARAWAK
2020

DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Malaysia Sarawak. Except where due acknowledgements have been made, the work is that of the author alone. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.

ROSDI

....

Signature

Name: Rosdi Anak Kira

Matric No.: 17020184

Faculty of Resource Science & Technology

Universiti Malaysia Sarawak

Date: 4th November 2020

ACKNOWLEDGEMENT

First and foremost, I want to praise God the Almighty, for giving me the spiritual strength throughout my postgraduate journey. His grace and mercies had given me strength, patience and determination in overcoming the challenges that had come upon me throughout this project.

I wish to express my sincere appreciation to my respected supervisor, Associate Professor Dr Lesley Maurice Bilung and co-supervisors, Professor Kasing Apun and Professor Lela Su'ut, for their full support and guidance in completing this project. Their guidance, patience, advices and supports enabled me to complete this research. It was a privilege and a great pleasure for me to be able to complete this project under their supervisions.

I would also like to extend my deepest gratitude to my other co-supervisor and mentor, Dr Romano Ngui for sharing his expertise and knowledge with me especially in the analytical phase of this study. He was the substance of a genius: he convincingly guided and encouraged me to be professional and keep on moving forward even when the journey got tough. Without his persistent motivation, I would not have been able to finish this project.

Last but not least, I wish to acknowledge the full support and great love from my family, especially my mother, Liah Anak Elaw; my sister and her husband: Meliny Anak Kira and Mohd. Hafiz Bin Jumaat. They supported me financially and kept me going on this project. This work would not have been possible without their input.

ABSTRACT

A diverse *Leptospira* serovars and reservoir hosts have been reported to circulate in various environmental settings in Sarawak. The risk of infection has been linked to socio-economic and environmental risk factors. This underscored the potential for a shift in the transmission dynamics of leptospirosis in Sarawak. It is imperative to consider the broad socio-demographical and environmental determinants such as climate and agricultural intensity, which may act as modifiable predictors for a disease like leptospirosis. These factors may be unevenly distributed, and their spatial distribution may influence the dynamics of leptospirosis. Hence, this study aims to determine the demographical and spatial distribution of leptospirosis using confirmed cases from 2011-2018 at a district level. This study also aims to investigate the global and localised relationship between leptospirosis with climate and agricultural variables. The demographical distribution of leptospirosis was analysed based on descriptive and inferential statistics by aggregating the data according to demographical groups. Spatial statistics including global and local Moran's *I* was employed to study the spatial autocorrelation of leptospirosis incidence rate by districts. The potential clustering of hot spot and cold spot regions were investigated using Getis-Ord-Gi* statistics. The relationship between environmental factors and spatial density of geocoded leptospirosis cases was explored by using global Poisson regression (GPR) and geographically weighted Poisson regression (GWPR). A total of 4,648 cases were reported from 2011-2018 with the highest incidence in 2018, with 31 cases per 100,000 population. One hundred and thirty-nine fatal cases were reported, with the overall case fatality rate of 2.99%. Higher incidence rate per 100,000 population was observed in males (35.79; 95% CI: 22.92- 48.67), individuals aged between 50-59 years (27.22; 95% CI: 15.91- 38.53), other Bumiputera ethnic group (32.21; 95% CI: 16.80-47.82) and elementary occupational type (56.93; 95% CI: 26.49-87.37). Overall, the leptospirosis incidence in Sarawak demonstrated a positive spatial clustering (Moran's *I*: 0.28) with significant positive local clustering observed in 2012 (Moran's *I*: 0.23), 2013 (Moran's *I*: 0.33) and the highest Moran's *I* in 2014 (0.45). An increasing incidence trend was observed towards the southeast region with a standardised incidence ratio (SIR) between 0.39 and 4.54. The southeast region was identified as a significant hot spot region (z-scores: 1.58 to 2.83). Leptospirosis in the hot spot region was concentrated in areas with higher water vapour pressure ($exp(\beta)$: 1.12; 95% CI: 1.02 - 1.25) and annual precipitation ($exp(\beta)$: 1.15; 95% CI: 1.02 - 1.31), with lower precipitation in the driest month ($exp(\beta)$: 0.85; 95% CI: 0.75 – 0.96) and the wettest quarter ($exp(\beta)$: 0.88; 95% CI: 0.77 – 1.00). Water vapour pressure (WVP) has the most variation effect across the hot spot region with a standard deviation of 0.62 (LQ: 0.15; UQ; 0.99) while least variation in effect was observed in annual precipitation (ANNP) with a standard deviation of 0.14 (LQ: 0.11; UQ; 0.30). The GWPR model explained better relationships between leptospirosis and environmental covariates as denoted by the reduction in AICc value from 519.73 to 443.49. The results of localised relationships presented in this study could be used to formulate spatially targeted interventions. This would be useful particularly in localities with strong environmental or socio-demographical determinants for the transmission leptospirosis.

Keywords: Environmental variables, geographically weighted Poisson regression, *Leptospira*, Moran's *I*, spatial autocorrelation

Penilaian Pembolehubah Alam Sebagai Faktor Risiko untuk Penularan <u>Leptospira</u> spp.

ABSTRAK

Pelbagai serovar dan haiwan pembawa telah dilaporkan beredar dipelbagai tetapan alam di Sarawak. Risiko jangkitan telah dikaitkan dengan faktor sosio-ekonomi dan alam sekitar. Hal ini menekankan potensi kepada perubahan dinamik jangkitan leptospirosis di Sarawak. Adalah amat penting untuk mengambil kira kepelbagaian faktor sosio-demografik dan alam sekitar seperti iklim and keamatan pertanian, yang boleh bertindak sebagai pembolehubah kepada penyakit seperti leptospirosis. Faktor-faktor tersebut juga mungkin tidak teragih secara sekata dan beredarannya yang tidak sekata mengubah dinamik leptospirosis. Oleh itu, kajian ini bertujuan untuk menentukan agihan demografik dan ruangan leptospirosis dengan menggunakan kes yang telah disahkan dari 2011-2018 pada peringkat mukim. Kajian ini juga berniat untuk mengkaji hubungan global dan tempatan diantara leptospirosis dengan pembolehubah iklim dan pertanian. Analisis mengenai agihan demografik telah ditentukan dengan statistic deskriptif dan inferensi, di mana data telah dikumpulkan mengikut kumpulan demografik. Statistik ruangan seperti Moran's I *global dan tempatan telah digunakan untuk mengkaji autokorelasi ruangan kadar insiden leptospirosis mengikut daerah. Kewujudan kluster tompok panas dan tompok sejuk telah dikaji menggunakan statistik Getis-Ord-Gi*. Hubungan diantara faktor alam dan kepadatan kes leptospirosis telah diteroka menggunakan regresi Poisson global (GPR) dan regresi Poisson berwajaran geografi (GWPR). Sebanyak 4,648 kes telah dilaporkan daripada tahun 2011-2018 dengan insiden tertinggi pada 2018, dengan 31 kes per 100,000 populasi. Seratus tiga puluh sembilan kes maut telah dilaporkan dengan kadar kematian sebanyak 2.99%. Insiden yang lebih tinggi telah dicatatkan oleh kaum lelaki 35.79 (95% CI 22.92- 48.67), kumpulan usia di antara 50-59 tahun (27.22; 95% CI: 15.91- 38.53), kumpulan etnik Bumiputera lain-*

lain (32.21; 95% CI: 16.80-47.82) dan kumpulan pekerjaan asas (56.93; 95% CI: 26.49-87.37). Keseluruhannya, insiden leptospirosis di Sarawak telah menunjukan kluster ruangan global yang positif (Moran's I*: 0.28) dengan kluster tempatan signifikan dicatatkan pada 2012 (Moran's* I*: 0.23), 2013 (Moran's* I*: 0.33) dan yang paling tinggi pada 2014 (0.45). Kenaikan aliran insiden telah dilaporkan ke arah tenggara dengan nisbah selaras insiden di antara 0.39 dan 4.54. Bahagian tenggara Sarawak telah dikenalpasti sebagai tompok panas yang signifikan (z: 1.58 to 2.83). Leptospirosis di tompok panas tertumpu pada kawasan yang mempunyai tekanan wap air (exp(β): 1.12; 95% CI: 1.02 - 1.25) dan jumlah hujan tahunan yang lebih tinggi (exp(β): 1.15; 95% CI: 1.02 - 1.31), dengan jumlah hujan pada bulan yang paling kering (exp(β): 0.85; 95% CI: 0.75 – 0.96) dan hujan pada suku tahun yang paling basah (exp(β): 0.88; 95% CI: 0.77 – 1.00) yang lebih rendah. Tekanan wap air mempunyai variasi kesan yang paling tinggi dengan sisihan piawai berjumlah 0.62 (LQ: 0.15; UQ; 0.99) manakala jumlah hujan tahunan mencatatkan variasi paling rendah dengan sisihan piawai 0.14 (LQ: 0.11; UQ; 0.30). Model GWPR telah mengesan hubungan di antara leptospirosis dan faktor-faktor alam dengan lebih terperinci berdasarkan penurunan angka AICc daripada 519.73 to 443.49. Hasil daripada hubungan setempat yang ditunjukkan dalam kajian ini dapat diguna untuk merumuskan strategi yang lebih terperinci. Ini amat penting terutamanya di kawasan yang mempunyai penentu alam atau sosio-demografik yang kuat.*

Kata kunci: *Faktor alam, regresi Poisson berwajaran geografi, Leptospira, Moran's* I*, autokorelasi ruangan*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AI	Annual Incidence
AICc	Corrected Akaike Information Criterion
ANNP	Annual Precipitation
arcmin	arcminute
arcsec	arcsecond
BIC	Bayesian Information Criterion
CHELSA	Climatologies at High Resolution for the Earth's Land Surface Areas
CI	Confidence Interval
CFR	Case Fatality Rate
CLD	Cropland Density
DIFF	Difference
EBK	Empirical Bayesian Kriging
ERDAS	Earth Resource Development Assessment System
ESRI	Environmental Systems Research Institute
exp	exponential
FAO	Food and Agricultural Organisation
GADM	Database of Global Administrative Areas
GIS	Geographical Information System
GLM	Generalised Linear Model
GLW	Gridded Livestock of the World
GPR	Global Poisson Regression
GRASS	Geographic Resources Analysis Support System

GWR	Geographically Weighted Regression
GWPR	Geographically Weighted Poisson Regression
GIS	Geographical Information System
HH	High-High type
HL	High-Low type
ILWIS	Integrated Land and Water Information System
km	kilometer
kPa	kilopascal
LH	Low-High type
LISA	Local Indicator of Spatial Autocorrelation
LL	Low-Low type
LPS	Lipopolysaccharide
LQ	Lower Quartile
LSD	Livestock Density
MAICE	Minimum AIC Estimator
MAT	Microscopic Agglutination Test
Max	Maximum
MDL	Minimum Description Length
ME	Mean Error
Min	Minimum
MSDE	Mean Standardised Error
MSE	Mean Standard Error
mm	milometer
MOH	Ministry of Health
NA	Not Available

OR	Odds Ratios
PDM	Precipitation in the Driest Month
PDQ	Precipitation in the Driest Quarter
Pr	Probability
PS	Precipitation Seasonality
PWM	Precipitation in the Wettest Month
PWQ	Precipitation in the Wettest Quarter
RMSE	Root Mean Square Error
RMSSDE	Root Mean Square Standardised Error
SD	Standard Deviation
SIR	Standardised Incidence Ratio
STH	Soil-Transmitted Helminthiases
SPSS	Statistical Package for Social Sciences
TS	Temperature Seasonality
UQ	Upper Quartile
VIF	Variance Inflation Factor
WGS	World Geodetic System
WHO	World Health Organisation
WVP	Water Vapour Pressure

CHAPTER 1

INTRODUCTION

1.1 Study background

Leptospirosis is regarded as one of the most important emerging zoonotic diseases with worldwide distribution (Haake & Levett, 2015). The World Health Organization (WHO) estimates the global burden of leptospirosis at over one million severe human cases per year, with a growing number of countries reporting leptospirosis outbreaks (Abela-Ridder et al., 2010; Hartskeerl et al., 2011). The causative organism is a spirochete bacterium in the genus *Leptospira*. Pathogenic *Leptospira* sp. is shed in bodily fluids of reservoir hosts, and infection occurs when the pathogen is transmitted directly and penetrates abraded skins or mucosal membranes, or through transmission via contaminated water bodies or environment. The sources of contamination are rodents, but a broad spectrum of domestic or wild animals can also be carriers of the pathogenic bacteria (Lau et al., 2010). Despite its apparent burden on human health and livestock productivity, the disease is one of the severely neglected tropical diseases (Dupouey et al., 2014). The varying clinical presentation of leptospirosis which often mimics other infectious diseases such as bacterial and viral hepatitis, influenza and malaria, may often lead to its under-reporting and misdiagnosis (Plank & Dean, 2000; Bharti et al., 2003; WHO, 2011; Crump et al., 2013). Outbreaks of leptospirosis have been reported from many regions around the world, but human infection is centred mainly in the tropical and subtropical regions with prominently high incidences in southeast Asia (Bahaman & Ibrahim, 1988; Kawaguchi et al., 2008; Al-shere et al., 2012; Hinjoy, 2016).

Leptospirosis is endemic in Malaysia, and it was gazetted as a notifiable disease since December 2010 under the Prevention and Control of Infectious Diseases Act 1988 (Ministry of Health Malaysia, 2011). The disease has continued to be a burden that significantly affects the Malaysian economy as well as the livelihood of citizens due to losses incurred from poor productivity in livestock, loss of jobs due to a reduction in the number of tourists visiting certain hot spots as well as costs of prevention and control (Garba et al., 2018). In the previous decade, there has been an upsurge of reported cases, with outbreaks primarily related to recreational activities and natural disasters (Hisham et al., 2009; Sapian et al., 2012). Risk factors including the proliferation of reservoir hosts, occupational and recreational exposure and occurrence of natural disasters have compounded the predisposition of humans to the risk of contracting leptospirosis in Malaysia (Garba et al., 2018). Climatic conditions are amongst the foremost factors for the endemicity and the persistence of leptospires in the natural environment across different geographical and ecological regions (Victoriano et al., 2009; Lau et al., 2010; Mwachui et al., 2015; Garba et al., 2018). Single outbreaks following the occurrence of extreme weather events in tropical countries such as Philippines, Laos, India and Malaysia have been deliberated in previous studies (Pappachan et al., 2004; Kawaguchi et al., 2008; Al-shere et al., 2012; Radi et al., 2018).

As urban and industrial development in Sarawak intensifies, new challenges may arise as an implication of induced ecological fragmentation and environmental changes. Ecological changes play a significant role in the emergence of infectious diseases, and urbanisation has been associated with outbreaks and the emergence of numerous infections around the world (Lau et al., 2010). Repercussions from land and natural forest clearing for rural development or agricultural expansion may have modified the distribution of zoonosis carriers such as rodents and mosquitoes. Rodent populations may expand to where people and settlements are clustered, so population density may be a proxy for leptospirosis risk in some areas. For instance, the establishment of large-scale oil palm estates in Sarawak has provided a feeding ground for rodents and brought them into closer proximity to human settlements. Such circumstance suggested an increase chance for the transmission of *Leptospira* spp. to humans.

In recent years, the use 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 discussions on integrating GIS analytics and geospatial statistics for environmental analyses of infectious diseases (Moore & Carpenter 1999). Previous studies have adopted GIS analysis tools in the development of ecological models to explore and analyse spatial variations between local environmental factors and occurrences of leptospirosis (Mohammadinia et al., 2017; Mayfield et al., 2018; Radi et al., 2018). Local modelling approaches, such as Geographically Weighted Regression (GWR) and Geographically Weighted Poisson Regression (GWPR) enable the exploration of local associations of variables (Fotheringham et al., 2003; Nakaya et al., 2005). GWPR has been used to study spatial variations in associations between health access, disease counts and risks, incidence rates, mortality risks and sets of socioeconomic characteristics (Nakaya et al., 2005; Cheng et al., 2011; Comber et al., 2011; Weisent et al., 2012; Odoi & Busingye, 2014). These studies explored the spatial pattern in the associations between a health outcome with a set of predictor variables and increase our understanding of how spatially varying risk factors can modulate health issues.

1.2 Problem statement

Sarawak Epid News reported that leptospirosis has escalated from 49 cases in 2010 to 616 cases in 2014, with a total of 53 deaths during that period (Sarawak Health Department, 2012). In this regard, the establishment of public health surveillance systems remain essential in achieving better control of this disease and should be parallel with the rapid industrialisation of Sarawak. Such manoeuvre would require an integration of multiple research disciplines including a comprehensive epidemiological study, sophisticated space-time monitoring of disease occurrence, and state of the art computer modelling to identify its underlying determinants. As an attempt to invest in disease prevention and control measures, it is imperative to consider the broad socio-demographical and environmental determinants, which may act as modifiable predictors for a disease like leptospirosis. These factors may be unevenly distributed, and their spatial distribution may influence the dynamics of leptospirosis. The ecological associations of diseases may vary geographically as covariates may change depending on different geographical contexts (Nakaya, 2005). Hence, these knowledge gaps hindered the formulation of reliable control measures and underscored the need for the establishment of site-specific intervention and emergency response.

When the understanding of leptospirosis transmission risk is uncertain, GIS technologies and spatial statistics offer tools to circumvent problems about spatial and temporal relationships in diseases with complex transmission cycle. GIS technologies can combine multiple site-specific metadata from humans, animals and environment for spatially rigorous analysis with an added advantage of interactive visual representation. Examples include the epidemiological application of data obtained from climate-based forecast systems like the observation of land cover, land use, elevation, oceans, surface temperatures