COMPARATIVE SPATIAL ANALYSIS OF ENTERIC FEVER AND LEPTOSPIROSIS IN KELANTAN, MALAYSIA USING E-NOTIFIKASI SURVEILLANCE DATABASE, 2016 – 2022

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DECLARATION

I declare this research project is my own work and has not been submitted for the award of a higher degree elsewhere.

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LIST OF DRAFT PAPER

This research project contains two draft papers:

1. Hazlienor Mohd Hatta, Kamarul Imran Musa, Nik Mohd Hafiz Mohd Fuzi, Paula Moraga. *Incidence, Spatial Distribution and Spatial Variation in Risk of Enteric Fever and Leptospirosis in Kelantan, Malaysia*. (Prepared for submission to the Osong Public Health and Research Perspectives Journal)
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LIST OF SYMBOLS

M	Metre
Km	Kilometre
km^2	Square kilometre
>	More than
<	Less than
%	Percentage

LIST OF ABBREVIATION

ANN	Average Nearest Neighbour
CDCIS	Communicable Diseases Control Information System
CI	Confidence Interval
CRS	Coordinate Reference System
CSR	Complete Spatial Randomness
CPRC	Crisis Preparedness & Response Centre
COVID-19	Coronavirus Disease 2019
DALYs	Disability-Adjusted Life Years
DIVC	Disseminated Intravascular Coagulation
DOSM	Department of Statistics Malaysia
ELISA	Enzyme-Linked Immunosorbent Assay
EWAR	Early Warning, Alert and Response
GLEAN	Global Leptospirosis Environmental Action Network
GPS	Global Positioning System
HFMD	Hand-Foot-Mouth Disease
ICU	Intensive Care Unit
IDE	Integrated Development Environment
IQR	Interquartile range
KDE	Kernel density estimation
LDH	Lactic Acid Dehydrogenase
LFA	Lateral Flow Assay
MAT	Microscopic Agglutination Test
MOH	Ministry of Health

NNI	Nearest Neighbour Index
PCR	Polymerase Chain Reaction
PPP	*planar point pattern*
RSO	Rectified Skewed Orthomorphic
SMR	Standardized Morbidity Ratio
SD	Standard Deviation
WGS	World Geodetic System 1984
WHO	World Health Organization
XDR	Extensively drug-resistant

PERBANDINGAN ANALISIS RUANGAN DEMAM KEPIALU DAN LEPTOSPIROSIS DI KELANTAN, MALAYSIA MENGGUNAKAN PANGKALAN DATA SURVELAN E-NOTIFIKASI, 2016 – 2022

ABSTRAK

Latar Belakang: Demam kepialu dan leptospirosis adalah antara punca utama bagi penyakit demam akut yang tidak dapat dibezakan disebabkan oleh jangkitan bakteria yang dikaitkan dengan komplikasi teruk dan kadar kematian yang lebih tinggi. Beban penyakit ini adalah tinggi di Malaysia, khususnya Kelantan. Diagnosis yang tepat adalah mencabar tanpa pengesahan makmal, dan walaupun pelbagai strategi kesihatan awam telah dilaksanakan, demam kepialu dan leptospirosis masih kekal endemik di Kelantan.

Objektif: Kajian ini bertujuan untuk menghuraikan demam kepialu dan leptospirosis dengan lebih terperinci untuk membantu dalam membezakan penyakit ini daripada penyakit lain seperti denggi dan malaria, untuk menyediakan maklumat mengenai taburan, magnitud, corak geografi, dan kawasan berisiko demam kepialu dan leptospirosis di Kelantan, serta untuk meneroka korelasi ruangan antara kedua-dua penyakit untuk membantu dalam membangunkan algoritma diagnostik, pengawasan penyakit dan strategi kawalan.

Metodologi: Kes demam kepialu dan leptospirosis yang disahkan oleh ujian makmal dan didaftarkan di Kelantan pada tahun 2016 sehingga 2022 telah diekstrak daripada pangkalan data dalam talian survelan pasif e-Notifikasi. Analisis deskriptif dan ruangan telah dijalankan termasuk pemetaan insiden dan taburan penyakit, analisis corak titik univariat dan pelbagai jenis, autokorelasi serta variasi risiko ruangan menggunakan pakej **spatstat**, **spdep**, **sparr**, **spatialEco** dan **ggplot2** di dalam RStudio IDE.

Keputusan: Sebanyak 212 kes disahkan demam kepialu dan 1106 kes leptospirosis telah dianalisis dalam kajian ini. Purata kadar insiden tahunan bagi tahun 2016-2022 adalah 0.016 setiap 1000 penduduk (95% CI: 0.011, 0.022) untuk demam kepialu dan 0.084 setiap 1000 penduduk (95% CI: 0.071, 0.097) untuk leptospirosis. Kes demam kepialu didapati jauh lebih muda daripada kes leptospirosis, tetapi tidak terdapat perbezaan jantina yang ketara. Kajian itu mengenal pasti tujuh kes yang dijangkiti kedua-dua penyakit pada masa yang sama, berlaku di kawasan terutama di mana kedua-dua penyakit adalah endemik. Kedua-dua penyakit tidak menunjukkan signifikan korelasi ruangan dengan kepadatan penduduk. Terdapat variasi yang ketara dalam taburan geografi bagi kes dan insiden demam kepialu serta leptospirosis. Kes demam kepialu didapati bertompok dengan titik panas kebanyakannya tertumpu di bahagian utara Kelantan. Taburan kes leptospirosis adalah seperti demam kepialu di wilayah utara tetapi menunjukkan intensiti ruangan yang lebih tinggi di bahagian selatan Kelantan dengan risiko ruangan yang lebih tinggi untuk leptospirosis berbanding demam kepialu. Leptospirosis menunjukkan autokorelasi ruangan secara positif dengan kelompok panas kebanyakannya diperhatikan di kawasan selatan dan tenggara. Kes demam kepialu juga didapati berkelompok bersama kes leptospirosis dalam jarak dua hingga sepuluh kilometer. Walaupun terdapat penurunan beransur-ansur dalam bilangan kes bagi kedua-dua penyakit dari 2016 hingga 2021, terdapat lonjakan kes ketara yang diperhatikan pasca pandemik COVID-19.

Kesimpulan: Memahami dinamik transmisi jangkitan di kawasam tempatan adalah penting kerana penularan penyakit berjangkit dipengaruhi oleh pelbagai faktor, yang membawa kepada variasi geografi dalam risiko jangkitan. Analisis ruangan mendedahkan corak taburan, pengelompokan dan lokasi titik panas untuk demam kepialu dan leptospirosis menunjukkan faktor risiko persekitaran dan sosio-ekonomi berkemungkin sama untuk kedua-dua penyakit. Intervensi yang disasarkan dan sistem amaran awal boleh dilaksanakan berdasarkan penemuan ini untuk meningkatkan strategi kawalan dan pencegahan penyakit. Penemuan kajian ini akan membimbing penggubalan dasar, protokol pengurusan, dan penyelidikan lanjut mengenai faktor sosio-persekitaran yang menyumbang kepada penyebaran penyakit

Kata kunci: Diagnosis; Demam kepialu; Kajian ruangan ; Kelantan; Leptospirosis

ABSTRACT

Comparative Spatial Analysis of Enteric Fever and Leptospirosis In Kelantan Using e-Notifikasi Surveillance Database, 2016 – 2022

Background: Enteric fever and leptospirosis are increasingly important bacterial causes of acute undifferentiated febrile illness associated with severe complications and higher fatality. The burden of these diseases is high in Northern Malaysia, particularly Kelantan State. Accurate diagnosis is challenging without laboratory confirmation, and despite various public health strategies implemented, enteric fever and leptospirosis remain endemic in Kelantan.

Objective: To provide information on the distribution, magnitude, geographical patterns, and risk areas of enteric fever and leptospirosis in Kelantan, and to explore the spatial relationship between the two diseases.

Methodology: Laboratory-confirmed enteric fever and leptospirosis cases registered in Kelantan between the years 2016 and 2022 were extracted from the national e-Notifikasi passive surveillance online database. Descriptive and spatial analyses were carried out including incidence and disease mapping, univariate and multitype point pattern analysis, spatial autocorrelation as well as spatial risk variation using **spatstat, spdep, sparr, spatialEco** and **ggplot2** R packages inside RStudio IDE.

Result: A total of 212 confirmed cases of enteric fever and 1106 cases of leptospirosis were examined in this study. The average annual incidence for the period of 2016-2022 was 0.016 per 1000 population (95% CI: 0.011, 0.022) for enteric fever and 0.084 per 1000 population (95% CI: 0.071, 0.097). Enteric fever cases were found to be significantly younger than leptospirosis cases, but there was no significant gender difference observed. The study identified seven cases of co-infection, primarily occurring in areas where both diseases were endemic. Both diseases did not show any spatial correlation with population density. Substantial geographical variation of enteric fever and leptospirosis was observed across the state. Enteric fever cases were significantly clustered, and hotspots were predominantly concentrated in the northern part of Kelantan. Leptospirosis cases were as intense as enteric fever in the northern region but exhibited higher spatial intensity in the southern part of Kelantan with higher spatial risk for leptospirosis compared to enteric fever. Leptospirosis was positively spatially autocorrelated with high-high clusters mostly observed in southern and southeastern regions. Spatial dependence between enteric fever and leptospirosis cases within two to ten kilometres distance was also demonstrated. Despite gradual declines in the number of cases for both diseases from 2016 to 2021, there were notable surges observed during the post-COVID-19 pandemic era.

Conclusion: Understanding local dynamics is crucial as infectious disease transmission is influenced by various factors, leading to geographical variations in infection risk. Spatial analysis revealed distribution patterns, clustering, and hotspot locations for both diseases, indicating common environmental and socio-economic risk factors for both diseases. Diagnostic algorithms, targeted interventions and early warning systems can be implemented based on these findings to improve disease control and prevention strategies.

Keywords: Diagnosis; Enteric Fever; Kelantan; Leptospirosis, Spatial analysis

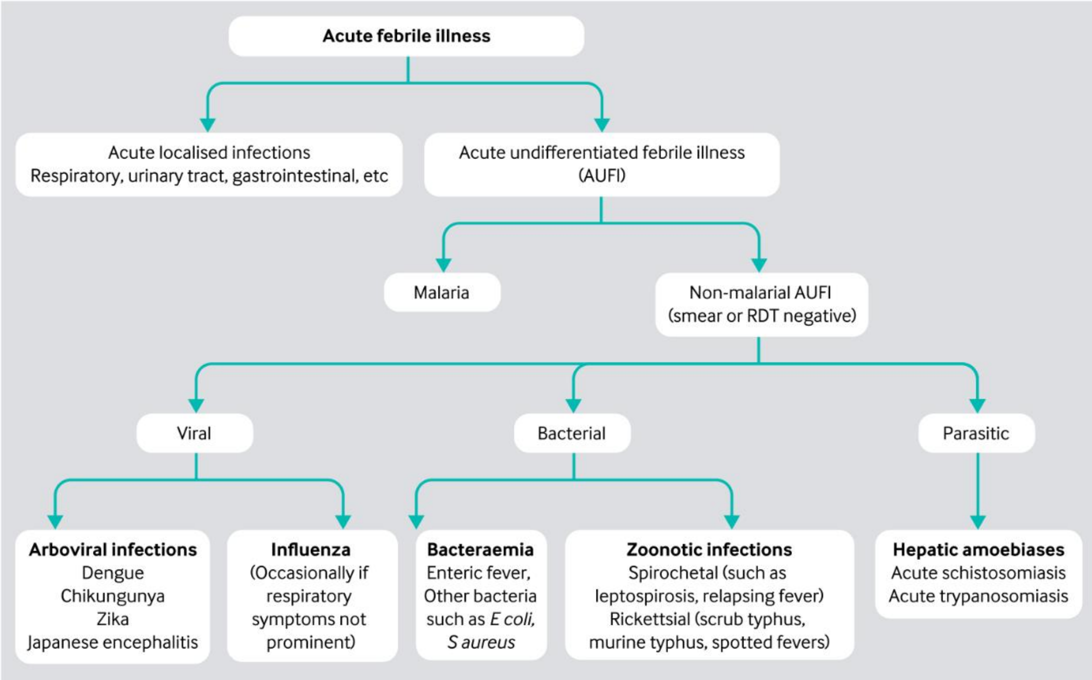
CHAPTER 1

INTRODUCTION

1.1 Study background

There is an increasing concern regarding emerging and re-emerging infectious diseases that cause undifferentiated febrile illness contributing towards substantial mortality and morbidity in children and adults (Wangdi *et al.*, 2019). At least one pathogen was identified among 41 - 73% of the hospitalized patients with febrile illness (Shrestha *et al.*, 2018). Replacing malaria as the recent common cause of febrile illness in tropical and sub-tropical regions are dengue, scrub typhus, leptospirosis and enteric fever (Bhargava *et al.*, 2018). However, bacterial aetiologies, mainly enteric fever and leptospirosis are significantly becoming important as they are often associated with more severe complications and higher fatality (Chipwaza *et al.*, 2015).

Leptospirosis is caused by pathogenic leptospiral spirochete whereas enteric fever is caused by *Salmonella enterica* serovar typhi and paratyphi A, B or C (Malaysia Ministry of Health, 2017). Other than vector-borne diseases that can be rapidly diagnosed in health facilities, and seasonal influenza, enteric fever and leptospirosis are the two predominant bacterial causes of undifferentiated febrile illness in the tropical region especially South and Southeast Asia (Bhargava *et al.*, 2018). Over 14 million enteric fever cases are reported worldwide while 30% of bacteraemia cases in Asia are caused by *S.* typhi (Deen *et al.*, 2012). Whereas leptospirosis contributed towards 3 million disability-adjusted life years (DALYs) with over 50,000 deaths reported annually (Torgerson *et al.*, 2015). The burden of enteric fever and leptospirosis are higher in Northern Malaysia, in which the latest incidence of enteric fever and leptospirosis in Kelantan reported in the pre-pandemic era was 0.5 and 16 per 100,000 population respectively. The presentation of these diseases is similar making accurate diagnosis difficult without laboratory confirmation (Wangdi et al., 2019). Despite various public health strategies being carried out, these two diseases remain endemic in Kelantan (Ho et al.,2022).



Source: Bhargava *et al.* (2018)

Figure 1.1 Broad classification of acute febrile illness depicting enteric fever and leptospirosis among the common bacterial causes of acute undifferentiated febrile illness in the tropical and subtropical regions.

1.2 Problem statement

Enteric fever and leptospirosis remain endemic in Kelantan contributing towards the major burden of infectious diseases, morbidity and mortality in this state, but the area of endemicity is not well described. These two diseases have similar clinical presentations, are often clustered due to their mode of transmission, are mediated by contaminated water and have overlapping socio-environmental risk factors. However, these diseases are being managed separately utilising intense resources.

The keys to the management of these diseases are early diagnosis and antibiotic treatment but differentiating one from another is a diagnostic challenge. However, it was found that only one-third of hospitalized leptospirosis cases in Northern Malaysia were accurately diagnosed, and often were misdiagnosed as typhoid. Co-infection of diseases is also of concern because it is frequently associated with atypical and more severe manifestations, particularly when the diseases are endemic in the same location. Rapid tests for both diagnoses aren't widely available in health facilities. Hence, with limited access to testing, clinicians may need to rely on a careful history and physical examination along with the epidemiological knowledge of the local agent and disease distribution to formulate a diagnosis and start the treatment.

Despite the advantages of spatial analysis in identifying susceptible populations, assisting in disease prediction, as well beneficial for control and prevention, spatial analysis is not customarily carried out by the public health offices and is not incorporated into the routine surveillance system or early warning system or being used to guide informed decisions.

1.3 Rationale of the study

Characterizing enteric fever along with leptospirosis would provide adequate information that would aid the clinician in differentiating these diseases from each other and other common causes of undifferentiated fever in this state such as dengue fever and malaria. Unlike these vector-borne diseases that are well studied and can be rapidly diagnosed at health facilities as rapid diagnostic tools are widely available, the recent information on the distribution of enteric fever and leptospirosis in this state is scarce. Coupled with the already available studies, this study would provide sufficient information to assist in developing a diagnostic algorithm for undifferentiated fever in this state.

This study will also provide an estimation of the magnitude of enteric fever and leptospirosis in this state based on age, gender, district and subdistrict, thus, allowing the identification of the susceptible population. The study will also be able to determine the geographical pattern of enteric fever and leptospirosis in Kelantan, thus, will assist in the identification of clustering of cases and risk areas of the studied diseases that could be integrated into the early warning, alert and response (EWAR) system for the disease surveillance.

As enteric fever and leptospirosis have an overlapping mode of transmission, contributing environmental factors and clinical features, this study will further provide evidence if there are any differences in geographical distribution between these two diseases in Kelantan. As these diseases have overlapping properties, if it’s found that these diseases are spatially correlated, not only could serve as predictors of the disease occurrence of each other but targeting similar environmental and other risk factors would substantially reduce the incidence of both diseases using the same approach.

This study would also provide proper estimates of the disease distribution and a better understanding of spatial variability at the subdistrict level that are essential for policymaking on developing management protocols as well as for targeted preventive and control measures in settings with limited resources. The findings from this study will also open up opportunities for further research to explore the socio-environmental and other factors that may contribute towards spatial variations of the studied diseases in Kelantan.

1.4 Research questions

1.4.1 What are the incidences of enteric fever and leptospirosis in Kelantan between the year 2016 - 2022?

1.4.2 What is the geographical distribution of enteric fever and leptospirosis in Kelantan?

1.4.3 What is the density of enteric fever and leptospirosis cases in Kelantan?

1.4.4 Are the enteric fever and leptospirosis cases in Kelantan clustered or randomly distributed?

1.4.5 Is there any relation between the geographical pattern of enteric fever and leptospirosis in Kelantan?

1.5 Objectives

1.5.1 General objective

The general objective of this study is to determine and compare the incidence and geographical distribution of enteric fever and leptospirosis in Kelantan, Malaysia using the year 2016 – 2022 surveillance data extracted from the e-Notifikasi system.

1.5.2 Specific objectives

1.5.2.1 To determine the overall and specific incidence based on gender, district and sub-district for enteric fever and leptospirosis in Kelantan using the year 2016 – 2022 surveillance data extracted from the e-Notifikasi system.

1.5.2.2 To map the spatial distribution of enteric fever and leptospirosis cases in Kelantan from the year 2016 – 2022.

1.5.2.3 To estimate the density of enteric fever and leptospirosis cases in Kelantan from the year 2016 – 2022.

1.5.2.4 To identify the spatial clustering of enteric fever and leptospirosis cases in Kelantan from the year 2016 – 2022.

1.5.2.5 To compare the spatial pattern and risk variation of enteric fever and leptospirosis cases in Kelantan from the year 2016 – 2022.

1.6 Research hypotheses

H_1 There is a significant spatial pattern or clustering of enteric fever and leptospirosis cases in Kelantan; the distribution of enteric fever and leptospirosis cases is not random and exhibits spatial clustering or deviation from complete spatial randomness.

There is a significant spatial relationship or association between enteric fever and leptospirosis cases in Kelantan. The spatial distribution of enteric fever cases is dependent on the spatial distribution of leptospirosis cases, suggesting that there may be a spatial correlation or interaction between these two diseases.

CHAPTER 2

LITERATURE REVIEW

This chapter provides a review of the epidemiology and presentation of enteric fever and leptospirosis, spatial data analysis and the framework of the study.

2.1 Natural history of enteric fever and leptospirosis

2.1.1 Enteric fever

Typhoid fever is caused by *Salmonella enterica* serovar typhi whereas paratyphoid fever is caused by *Salmonella enterica* serovar paratyphi A, B (*S.*Schottmülleri), or C (*S.*Hirschfeldi*i*); both are collectively termed as enteric fever (World Health Organization, 2018). *Salmonella* typhi and paratyphi A, in particular, are highly adapted to their human host in which nearly five per cent of the infected individuals may become asymptomatic chronic carriers, and if unidentified and treated, they may become the reservoir and continue to spread the disease to others (World Health Organization, 2018). The ability of *S.* paratyphi B strains to ferment tartrate distinguishes them into two distinct pathotypes: the first pathotype, *S.* paratyphi B, is unable to ferment tartrate and is associated with paratyphoid fever; the second pathotype, *S.* paratyphi B variant L(+) tartrate(+), ferments tartrate and is associated with gastroenteritis typical of nontyphoidal salmonellosis (Nemhauser, 2023).

Human is the only host for *Salmonella* Typhi and paratyphi A while paratyphi B and C have been isolated from animals (World Health Organization, 2018). In short-cycle transmission, enteric fever is contracted by ingesting water or food contaminated with the faeces of an acutely infected or convalescent individual, or a person with chronic, asymptomatic carriage within the immediate environment (World Health

Organization, 2018). In endemic low- and middle-income nations with limited access to healthy food and water, as well as poor sanitation, the risk of infection is substantial (Nemhauser, 2023). Sexual contact has been recorded as an unusual route of transmission, notably among men who have sex with men (Nemhauser, 2023). However, in a long-cycle transmission, the contamination may involve a broader environment, such as human faeces polluting untreated water supplies, or the use of human faeces or untreated sewage as agricultural fertiliser (Crump, 2019).

The incubation period for enteric fever is between 6 to 30 days. The clinical presentation of enteric fever varies especially in the initial stage in which the symptoms are vague and may resemble other diseases. The onset is often insidious, with gradually worsening fatigue, followed by a stepladder pattern of low-grade fever by the third or fourth day. Other symptoms include anorexia, headaches, malaise, abdominal pain, constipation or diarrhoea, vomiting, myalgia, sore throat, or even dry cough (Nemhauser, 2023). Liver involvement with jaundice or hepatosplenomegaly is frequently found (Nemhauser, 2023). Occasionally, rose-coloured maculopapular rashes may be observed on the trunk (Nemhauser, 2023). However, these pathogens are only sensitive to specific antimicrobial treatments which if delayed or left untreated, may cause severe complications. Without prompt treatment, around 10% of typhoid patients will develop major complications such as colitis or intestinal perforation, meningitis, psychosis, myocarditis, disseminated intravascular coagulation (DIVC), hemolytic uremic syndrome, shock, and coma, with a case fatality rate of 1-4% (Nemhauser, 2023). Although paratyphoid fever is relatively less severe compared to typhoid fever, the infection is invasive and could potentially cause 1-10% of severe complications with the possibility of progressing to a chronic carrier state (Teh *et al.*, 2014). Relapse occurs in up to 10% of untreated patients approximately 1 to 3 weeks after recovering from the initial illness (World Health Organization, 2018).

Typhoid fever has also become increasingly resistant to antibiotics over the past 50 years. Fluoroquinolones, the mainstay against multidrug-resistant *S*. typhi in the 1990s, became ineffective by the 2010s. In 2021 resistance to azithromycin was found to have arisen in several *S*. typhi strains, threatening the efficacy of all oral antimicrobials for typhoid treatment (Da Silva *et al.*, 2022)

2.1.2 Leptospirosis

Leptospirosis is a re-emerging zoonosis caused by species of Gram-negative spirochaete bacterium belonging to the Leptospiraceae family from *Leptospira genus*, which has a rising genetic diversity, with 38 species of pathogenic Leptospira discovered so far (Cilia et al., 2021). The genus Leptospira was traditionally separated into two species: pathogenic *L. interrogans* and saprophytic *L. biflexa*. There are around 60 serovars of the *L. biflexa* species, and over 200 of the *L. interrogans* species (Cilia *et al.*, 2021). Pathogenic Leptospira causes moderate to severe forms of the disease, whereas intermediate Leptospira causes less severe infections. Saprophytic serovars, on the other hand, are not regarded as harmful unless they undergo genetic recombination processes with pathogenic serovars (Cilia *et al.*, 2021). Despite being a microaerophile, *Leptospira* grows well even under complete aerobiosis conditions. It grows optimally at temperatures between 28 and 30 ^{o}C with the ideal pH ranging from 7.2 to 7.4 (Harran *et al.*, 2022).

Leptospirosis can be found globally, in both rural and urban areas, and temperate and tropical climates. The reservoir is mainly animal with rats as the major reservoir, causing asymptomatic illness with *Leptospira* colonisation in renal tubules and excretion in the environment via urine (Picardeau, 2013). Other mammal species, both wild and domestic such as dogs, horses, cattle, and swine could serve as reservoirs (Nemhauser, 2023). Bacterial transmission to humans occurs through direct contact with infected animal urine, reproductive fluid, blood, or tissue, or, more frequently, through exposure to a contaminated environment including consumption of contaminated food or water (Picardeau, 2013). Following contact with contaminated water, *Leptospira* enters the human body through skin lesions or mucosa of the eyes, mouth, or nose (Picardeau, 2013).

The average incubation period is 7-12 days, ranging from 3 – 29 days (Haake and Levett, 2015). The septicaemic or acute stage of leptospirosis begins in the first week of infection and is characterised by unspecified symptoms and signs of bacteraemia including acute onset of fever, nausea, vomiting, diarrhoea, body ache, chills and headache, while conjunctival suffusion has also been commonly reported (Soo *et al.*, 2020; Harran *et al.*, 2022). The second stage of the disease is the immunological stage, which typically occurs in the second week of infection and is characterised by the host's acquisition and expression of anti-Leptospira antibodies in the serum that may lead to severe complications such as sepsis-like syndrome, Weil’s disease characterized by haemorrhage, jaundice and renal failure, thrombocytopenia, liver and other organ failure or even death (Soo *et al.*, 2020; Harran *et al.*, 2022). Most leptospirosis illnesses are mild and spontaneously resolved (Haake and Levett, 2015). Early oral antibiotic therapy such as azithromycin or amoxicillin may prevent the progression to more severe illness requiring parenteral penicillin, ampicillin, cefotaxime or ceftriaxone (Haake and Levett, 2015).

2.2 Burden of enteric fever and leptospirosis

2.2.1 Global burden of enteric fever and leptospirosis

Enteric fever and leptospirosis are being constantly reported as the common bacterial causes of acute undifferentiated febrile illness in tropical and subtropical regions. A systematic review by Wangdi *et al.* (2019) analysing acute febrile illness in Asia estimated the overall prevalence of leptospirosis and typhoid around 4% each in the continent and listed leptospirosis as the main cause of undifferentiated fever among outpatients in Southeast Asia with a prevalence of 12.1%. Whereas, in India, the prevalence of leptospirosis and enteric fever among febrile cases were found to be 21% and 17% respectively; higher than dengue fever at 8% (Sushi *et al.*, 2014).

Each year, an estimated 11-21 million cases of typhoid fever and 5 million cases of paratyphoid fever are reported worldwide, resulting in 135,000-230,000 deaths (Nemhauser, 2023). The burden of enteric fever is found to be higher in South and Southeast Asia; the global pooled incidence rate of enteric fever was estimated to be 197.8% (95% CI: 172.0, 226.2) and highest in Southeast Asia at 219.8 (95% CI: 192.9, 249.1) per 100,000 person-years in 2017 with over 14.3 million cases were reported throughout that year (Stanaway *et al.*, 2019).

As for leptospirosis, around 1.3 million (95% CI: 0.43, 1.75) cases and 59,000 deaths were reported worldwide each year; the highest incidence was reported in South and Southeast Asia, Oceania, Caribbean, Andean, Central and Tropical Latin America, and East Sub-Saharan Africa; in which this disease was also commonly reported among travellers (Costa *et al.*, 2015).

2.2.2 Local burden of enteric fever and leptospirosis

Both enteric fever and leptospirosis are mandatory notifiable diseases in Malaysia. The recent incidence of enteric fever in Malaysia before the pandemic COVID-19 era was 15.4 per 100,000 population; higher in Kelantan and Pahang (Ho *et al.*, 2022). Despite the decreasing incidence of enteric fever in this country for the past decade, it remains endemic in Malaysia's east coast (Muhammad *et al.*, 2020).

Meanwhile, the incidence of leptospirosis in Malaysia is specifically higher in Kelantan, Selangor, Sarawak, Kedah and Terengganu (Yaakob *et al.*, 2015). The incidence of leptospirosis in this country rose from 1.03 cases per 100, 000 population in 2004 to 30.2 cases per 100,000 in 2015 (Fann *et al.*, 2020). The number of leptospirosis cases in this country was staggeringly high in the past decade, with 1976 cases and 69 deaths reported in 2010 and rose to 7806 cases in 2014 before gradually decreasing (Soo *et al.*, 2020).

2.2.3 Age distribution of enteric fever and leptospirosis

The incidence of enteric fever was found to be highest in the paediatric age group, peaking among 5-9 years old children and further declining with age; 12.6% (95% CI: 8.7, 17.7) cases were among children less than 5 years old while 55.9% (95% CI: 50.3, 61.6) were aged less than 15 years old (Stanaway *et al.*, 2019). This is consistent with another study by Dewan *et al.* (2013) that documented the highest incidence among children <5 years old. However, Saha *et al.* (2019) documented a bimodal age distribution of 1-7 years and 17-28 years age group but over half of the enteric fever cases were diagnosed among children <5 years old. In Kelantan, the prevalence of enteric fever was highest among children aged <2 years old and teenagers (Ho *et al.*, 2022). Whereas, Costa *et al.* (2015) reported a large proportion of leptospirosis cases occurred in adults aged 20-49 years old. In Malaysia, leptospirosis patients aged 70 years and above were associated with higher fatality (Philip *et al.*, 2021).

2.2.4 Gender distribution of enteric fever and leptospirosis

Literature has consistently reported male predominance for enteric fever (Medhat and Aljanabay, 2022). Some studies demonstrated higher cases of enteric fever occurring in females especially when it is associated with household activities such as cooking and washing, but the incidence of complications such as intestinal perforation was found to remain higher among males (Khan, 2012). However, both gender was found to be equally affected by enteric fever in Malaysia (Afar *et al.*, 2013). In general, leptospirosis predominantly affects males (Haake and Levett, 2015) but the incidence of leptospirosis was also found to be high among adult females (Daher and da Silva Junior, 2020). This was also in line with a cross-sectional study by Mansoor (2020) done in Bangladesh that demonstrated a higher incidence among adult females. In Malaysia, leptospirosis patients were predominantly male (Philip *et al.*, 2021).

2.3 Diagnosis of enteric fever and leptospirosis

Several laboratory methods are being used for the leptospirosis diagnosis, mainly the time-consuming and laborious Microscopic Agglutination Test (MAT) and Polymerase Chain Reaction (PCR) with longer laboratory turnaround time in comparison to Enzyme-Linked Immunosorbent Assay (ELISA) and Lateral Flow Assay (LFA) (Yaakob *et al.*, 2015). Whereas, the gold standard diagnosis for enteric fever is by isolation of *Salmonella* typhi or paratyphi from clinical specimens via culture (Malaysia Ministry of Health, 2017). There are also currently available rapid tests available for detecting typhoid and paratyphoid A including Typhidot and immunochromatographic lateral flow assay (Wijedoru *et al.*, 2017).

2.4 Environmental factors of enteric fever and leptospirosis

The distribution of enteric fever and leptospirosis may vary depending on the geographical location affected by the socio-demographic features, contributing environmental factors, prevailing species and strains (Philip *et al.*, 2021). A systematic review by Mogasale *et al.* (2014) listed urbanisation, population density, poor sanitation, food and water contamination, living near water bodies like lakes and rivers, along with heavy rainfall, flood and warm temperatures as factors that favour the transmission of enteric fever.

Other than occupational exposure such as among farmers, sewer, animal traders and town cleaners, leptospirosis is also associated with heavily populated areas, poor housing conditions, lack of safe-water treatment, poor environmental hygiene, contact with water bodies, flood and heavy rainfall (Garba *et al.*, 2018). The rodent was identified as among the major reservoirs of leptospirosis, but complete rodent control was found to be difficult to achieve involving a collaboration of multiple sectors and extensive resources. The Global Leptospirosis Environmental Action Network (GLEAN) also outlined the importance of improving the water distribution and sanitation systems to prevent the transmission of the disease through cost-effective and sustainable solutions (Durski *et al.*, 2014).

2.5 Spatial analysis of infectious disease

2.5.1 Spatial analysis of enteric fever and leptospirosis

Infectious diseases differ geographically and by population, and they evolve over time. As infectious disease often exhibits distinct geographical features, spatial analysis done in several countries has been helpful in assessing spatial risk for enteric fever and leptospirosis incidence to derive appropriate health policy. The spatial analysis of enteric fever done in Jiangsu province of China found that the disease is spatially clustered, in which interventions were then strengthened at the hotspot areas and surroundings (Cheng *et al.*, 2013). Whereas the spatial analysis of typhoid fever in rural areas of Cambodia provides findings that suggested the location that needs to be prioritized for Vi conjugate vaccines among school children (Pham Thanh *et al.*, 2016). Another spatial analysis in India was able to characterize the areas with high enteric fever burden that supported the targeted approach of the typhoid vaccination programme (Cao *et al.*, 2021). However, a published study of spatial analysis of enteric fever in Kelantan in 2012 only analysed cases from four main districts with the highest distribution of cases (Saito *et al.*, 2012).

Another spatial analysis of leptospirosis in Kelantan generated a disease risk map based on the Standardized Morbidity Ratio (SMR) and Poisson-Gamma model but only at the district level and involved cases in 2016 only with no further point-pattern analyses or spatial autocorrelation done (Awang and Samat, 2017). In addition, spatial studies of leptospirosis in Kelantan are often associated with the major flood in 2014 (Radi *et al.*, 2018). Despite sharing similar properties, there is no study analysing the dynamics between these two diseases.

2.5.2 Spatial methods for infectious disease analysis

A variety of spatial methods would reveal overall clustering as well as a localized hotspot. Exploration of different clustering methods is essential to build complexity into spatial models of a disease process. The distribution of diseases can be analysed in the form of point or aerial data. Density-based techniques characterize the first-order pattern of the spatial distribution concerning the variation of the density of the observation across a study area (Gimond, 2023). Density-based spatial clustering analysis such as quadrat-based methods shows varying point densities at different locations in the study area while measures like Kernel density estimation (KDE) are useful to transform discrete observations into continuous variables (Lin *et al.*, 2011; Lin and Wen, 2022). Whereas distance-based measures analyse the second-order properties of the spatial distribution of observations using distances between point pairs that describe how the observations influence one another (Yuan *et al.*, 2020). The Average Nearest Neighbour Index (NNI) identifies if there is statistical evidence of clustering and therefore hotspot but provides limited information about the complexity of point patterns at different spatial scales; *F*-, *G*- *K*- and *L*-function described more detailed variations of a point pattern (Yuan *et al.*, 2020; Gimond, 2023).

Spatial autocorrelation describes the degree to which one object is similar to other nearby objects in which positive spatial autocorrelation might suggest infectiousness while negative autocorrelation can suggest a dispersal or transmission scale or differences in treatment facilities among different regions (Robertson and Nelson, 2014). Common measures include the Getis ord Gi* statistic that compares the local average to the global average as well as Moran's Index and Geary's *C* that also identify spatial outliers (Anselin, 2020).

The spatial relationship between two different diseases or conditions has also been studied. The bivariate Ripley's (cross) *K*-function has been used by (Said *et al.*, 2021) that examine the relationship between Hand-Foot-Mouth Disease (HFMD) and vaccine refusal cases. Lee's L statistic has also been used to test whether the spatial pattern of an attribute is similar to another (Kim, 2018).

2.6 Conceptual framework

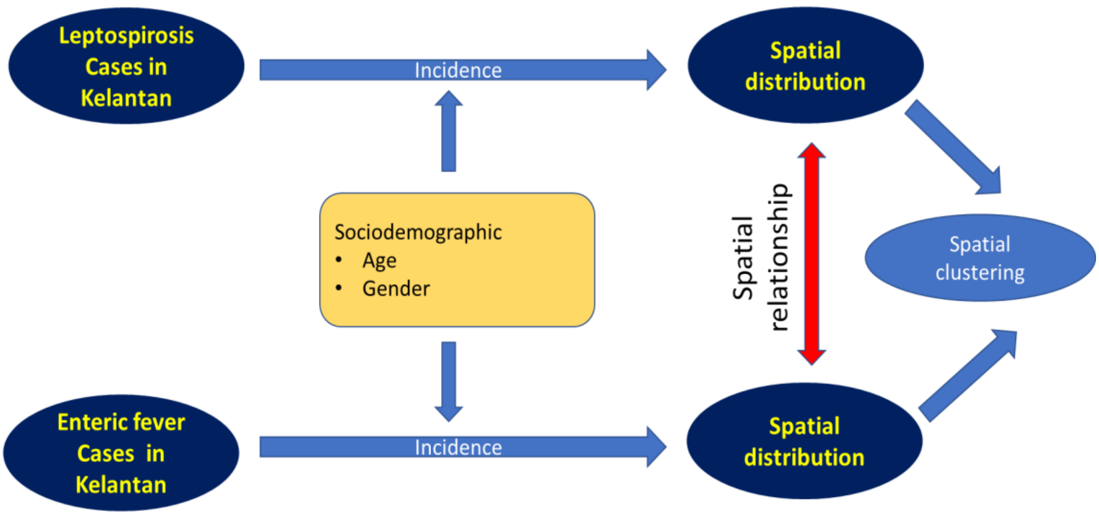


Figure 2.1 Conceptual framework for the comparative spatial analysis of enteric fever and leptospirosis in Kelantan between 2016-2022.

In this research, we aim to investigate the incidence and spatial distribution of enteric fever and leptospirosis in Kelantan, with a particular emphasis on how sociodemographic factors may influence the occurrence of these diseases. Our framework will involve a multi-faceted approach, integrating geospatial analysis, epidemiological data, and sociodemographic variables to elucidate the intricate relationships between disease incidence and various sociodemographic factors such as gender, and population density. Additionally, we will explore the spatial relationship between enteric fever and leptospirosis to determine if there are geographical factors or environmental conditions that may contribute to the co-occurrence or clustering of these diseases.

CHAPTER 3

INCIDENCE, SPATIAL DISTRIBUTION AND SPATIAL VARIATION IN RISK OF ENTERIC FEVER AND LEPTOSPIROSIS IN KELANTAN, MALAYSIA

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3.1 Abstract

Background: Differentiating enteric fever from leptospirosis and other causes of febrile illness in endemic areas is crucial to prevent unfavourable sequelae but is challenging without widely available rapid diagnostic tests. Misdiagnosis and co-infections are common in endemic areas while over-diagnosis leads to antibiotic resistance. Spatial analysis plays a crucial role in visualizing disease distribution, identifying high-incidence areas, and assessing vulnerability based on geographical and socioeconomic factors, ultimately aiding in disease differentiation and diagnosis.

Objective: To determine the incidence and characterized the spatial distribution as well as spatial risk variation of enteric fever and leptospirosis in Kelantan.

Methods: All laboratory-confirmed enteric fever and leptospirosis cases registered in Kelantan between 2016-2022 were extracted from the Communicable Disease Control Information System (CDCIS) e-Notifikasi online database and retrospectively reviewed. Crude incidence, point pattern analysis, and spatial risk variation analysis including disease and incidence mapping were carried out using **spatstat, spdep, sparr** and **ggplot2** R packages inside RStudio IDE.

Results: A total of 212 laboratory-confirmed enteric fever and 1106 leptospirosis cases were analysed. The average annual incidence for the period of 2016-2022 was 0.016 per 1000 population (95% CI: 0.011, 0.022) for enteric fever and 0.084 per 1000 population (95% CI: 0.071, 0.097). Enteric fever cases were significantly younger than leptospirosis cases but no significant gender predominant was observed. However, the incidence of leptospirosis was significantly higher in males at 0.110 per 1000 population (95% CI: 0.091, 0.133) compared to females at 0.055 per 1000 population (95% CI: 0.042, 0.072). Both diseases were found to be not spatially correlated with the population density. Enteric fever cases were concentrated in the northern part, notably within Kota Bharu and surrounding areas. Leptospirosis cases were as intense as enteric fever in northern Kelantan, but spatially more intense in the southern part where the spatial risk for leptospirosis was two to six times higher than enteric fever. There were seven cases of co-infection identified mostly from areas that were endemic for both. Despite a gradual decline of both diseases between 2016-2021, surges of cases were observed during post COVID-19 pandemic era.

Conclusion: This study offers valuable local epidemiological and spatial information on the endemicity of enteric fever and leptospirosis, aiding prompt diagnosis and resource allocation in differentiating the causes of acute undifferentiated febrile illnesses in Kelantan.

Keywords: Diagnosis; Enteric Fever; Kelantan; Leptospirosis, Spatial Analysis

3.2 Introduction

There is an increasing concern regarding emerging and re-emerging infectious diseases that cause undifferentiated febrile illness contributing towards substantial mortality and morbidity in children and adults (Wangdi *et al.*, 2019). The recent common causes of febrile illness in tropical and sub-tropical regions are dengue, scrub typhus, leptospirosis and enteric fever (Bhargava *et al.*, 2018). However, bacterial aetiologies, mainly enteric fever and leptospirosis are becoming important as they are often associated with more severe complications and higher mortality (Chipwaza *et al.*, 2015). Leptospirosis is caused by pathogenic leptospiral spirochete whereas enteric fever is caused by *Salmonella enterica* serovar typhi and paratyphi A, B or C (Malaysia Ministry of Health, 2017).

The keys to reducing the mortality and morbidity of these bacterial diseases are early diagnosis and initiation of appropriate antimicrobial treatment. It was reported that a substantial decrease in mortality of leptospirosis when the antibiotic is administered within 5 days after onset (Daher and da Silva Junior, 2020). However, diagnosis of leptospirosis and enteric fever are particularly difficult as the clinical symptoms are vague, especially in the initial course of the illness, and are often diagnosed late when the patient already developed complications (Samrot *et al.*, 2021). Hence, differentiating enteric fever from leptospirosis and other cause of febrile illness in endemic areas is a diagnostic challenge especially when rapid diagnostic tests are not widely available in health facilities. Misdiagnosis is common and co-infection has been constantly reported especially when the diseases are endemic in the same area (Wijedoru *et al.*, 2017). Over-diagnosis is also of concern as this can lead to inappropriate and excessive antibiotic use that contributes towards drug resistance. Extensively drug-resistant (XDR) typhoid is becoming a major public health issue;

over half of the recent typhoid fever cases in Pakistan were found to be sensitive only to azithromycin (Akram *et al.*, 2020).

Several laboratory methods are being used for the leptospirosis diagnosis, mainly the limited, time-consuming and laborious Microscopic Agglutination Test (MAT) and Polymerase Chain Reaction (PCR) with longer laboratory turnaround time in comparison to Enzyme-Linked Immunosorbent Assay (ELISA) and Lateral Flow Assay (LFA) (Yaakob *et al.*, 2015). Although ELISA and LFA produce rapid results at a cheaper cost and require less expertise, the sensitivity and specificity of these tests are lower compared to confirmatory MAT and PCR, hence, only regarded as screening tests (Yaakob *et al.*, 2015). Rapid tests are also not widely available in health facilities unlike for other causes of tropical febrile illness such as dengue fever and malaria (Yaakob *et al.*, 2015). The use of LFA also is limited to geographical locations as it only tests for a few common serovars out of over 250 available serovars of pathogenic Leptospira (Yaakob *et al.*, 2015). Whereas, the gold standard diagnosis for enteric fever is by isolation of *Salmonella* typhi or *Salmonella* paratyphi from clinical specimens via cultures that are also limited with a longer turnaround time (Malaysia Ministry of Health, 2017).

Kelantan is located in the north-eastern peninsular Malaysia, where enteric fever and leptospirosis are still endemic, contributing to the state's significant burden of infectious illnesses, morbidity, and death, but the area of endemicity is poorly defined (Garba *et al.*, 2018). Only 31.0% of hospitalized leptospirosis cases in Northern Malaysia were accurately diagnosed, and 7.1% were misdiagnosed as typhoid (Rafizah *et al.*, 2012). Co-infection of diseases associated with atypical and more severe presentation has also been reported in endemic areas (Rafizah *et al.*, 2012; Sushi *et al.*, 2014). With limited access to testing, clinicians may need to rely on a