THE RELATIONSHIP BETWEEN *PLASMODIUM KNOWLESI* MALARIA DISTRIBUTION AND ENVIRONMENTAL FACTORS IN KELANTAN

DR. KU MOHD SAIFULLAH BIN KU ISMAIL

UNIVERSITI SAINS MALAYSIA

2023

THE RELATIONSHIP BETWEEN *PLASMODIUM KNOWLESI* MALARIA DISTRIBUTION AND ENVIRONMENTAL FACTORS IN KELANTAN

By

DR KU MOHD SAIFULLAH BIN KU ISMAIL

Dissertation submitted in

partial fulfilment of the requirements

for the degree of

Doctor of Public Health (Epidemiology)

AUGUST 2023

ACKNOWLEDGEMENT

In the name of Allah, the most compassionate and the most merciful. Salutations upon His messenger Muhammad S.A.W (peace be upon him), his family, and his companions. With the blessings and guidance of Allah, I was able to complete this research just in time. I would like to express my sincere gratitude and appreciation to the individuals who have generously contributed and supported me in various capacities throughout conducting this study.

This research would be impossible without the support and encouragement of my supervisor, Associate Professor Dr. Nor Azwany Yaacob, and my co-supervisor, Professor Dr. Kamarul Imran Musa, Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia. I would like to express my appreciation to them for their contribution to making this research project possible. Their expertise, kindness, and patience are truly admirable.

Many thanks to my co-researcher, Dr. Ahmad Syaarani Yasin, Principal Assistant Director of the Vector Control Unit, Kelantan State Health Department, for his support in helping my work a lot more conducive.

I would like to acknowledge all my colleagues and lecturers in the Department of Community Medicine who are indirectly involved in this research project.

Indeed, I would greatly appreciate the support of my beloved spouse, family, and parents to make this work a success. I am deeply thankful to all of them.

TABLE OF CONTENTS

DECLARATION

I, Ku Mohd Saifullah bin Ku Ismail, declare that the thesis has been composed by myself in the manuscript-based thesis writing as an alternative format approved by the School of Medical Sciences, Universiti Sains Malaysia, and the work as not been submitted for an other degree or professional qualification. I confirm that the work presented in this thesis is originally mine. The information which has been derived from other sources is indicated in the thesis. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

Ku Mohd Saifullah bin Ku Ismail

Student ID: P-UD 0009/20

Signed on 14th August 2023

LIST OF PAPERS AND CONFERENCES

During my Doctor of Public Health (DrPH) course, the following articles were finally drafted for submission to the Web of Sciences Journal and/or presented at the international level. Overall, the thesis comprises the three drafted papers corresponding to the study's specific objectives.

Submitted manuscripts:

1. **Spatial And Temporal Clustering of *P. knowlesi* Malaria in Kelantan: A Point Pattern Analysis From 2012-2021**

   Ku Mohd Saifullah KI[1], Nor Azwany Y[1], Kamarul Imran M[1], Ahmad Syaarani Y[2]

   Submitted to the Journal of Preventive Medicine & Public Health, on 14th June 2023.

2. **The Relationships Between Climates and Relative Risk of P. knowlesi Malaria in Kelantan: A Time Series Analysis Using Distributed Lag Non-Linear Model**

   Ku Mohd Saifullah KI[1], Nor Azwany Y[1], Kamarul Imran M[1], Ahmad Syaarani Y[2]

   Submitted to the Tropical Medicine & International Health, on 14th June 2023.

3. **Mapping of *P. knowlesi* Malaria Incidence in Kelantan: A Geostatistical Modeling Using INLA**

   Ku Mohd Saifullah KI[1], Nor Azwany Y[1], Kamarul Imran M[1], Ahmad Syaarani Y[2], Paula Moraga[3]

Submitted to the Geospatial Health, on 25th June 2023.

[1]Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[2]Vector Unit, Disease Control Section, Kelantan State Health Department, 15200 Kota Bharu, Kelantan, Malaysia.

[3]Computer, Electrical and Mathematical Sciences and Engineering Division, King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia.

Conference Presentation:

9th UNIMAS Public Health Seminar 2023, Universiti Malaysia Sarawak, Kuching, Sarawak (e-conference), 8-9 March 2023.

1. Spatial and Temporal Intensity of *P. knowlesi* Malaria Cases in Kelantan (3rd place winner, Oral presentation)
2. Identification of Health Clinic in Kelantan with High Burden of *P. knowlesi* Malaria Cases: A Spatial Aggregation Methods (Poster presentation)

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AdjOR	Adjusted Odds Ratio
BCI	Bayesian Credible Interval
BFMP	Blood Films for Malaria Parasites
CI	Confident Interval
df	Degree of Freedom
DIC	Deviance Information Criterion
DLNM	Distributed Lag Non-linear Model
G6PD	Glucose-6-Phosphate Dehydrogenase
GIS	Geographic Information System
HC	Health Clinic
INLA	Integrated Nested Laplace Approximation
IQR	Interquartile Range
IRR	Incidence Rate Ratio
MCMC	Markov Chain Monte Carlo
P. falciparum	*Plasmodium falciparum*
P. knowlesi	*Plasmodium knowlesi*
P. malariae	*Plasmodium malariae*
P. ovale	*Plasmodium ovale*
P. vivax	*Plasmodium vivax*
OR	Odds Ratio
PCR	Polymerase Chain Reaction
qAIC	Akaike information criteria for quasi-poisson
SD	Standard Deviation

SPDE	Stochastic Partial Differential Equation
TAR	Mean Temperature Annual Range
WAIC	Watanabe-Akaike Information Criterion
WHO	World Health Organization
WVP	Water Vapor Pressure

LIST OF SYMBOLS

$>$	More than
$<$	Less than
$\geq$	More than or equal to
$\leq$	Less than or equal to
$=$	Equal to
%	Percentage
σ^2	Variance
$\|.\|$	Euclidean distance between two locations
K_ν	Modified Bessel function of the second kind and ν order
n	Number of populations
°C	Celsius
m	Meter
mm	Millimeter
m/s	Meter per second
km^{-2}	Per kilometer squared
Pa	Pascal
$f(x)$	Probability density function
$P(x_i)$	True *P. knowlesi* malaria incidence
$S(x_i)$	Spatial random effect

ABSTRAK

HUBUNGAN ANTARA TABURAN MALARIA *PLASMODIUM KNOWLESI* DENGAN FAKTOR PERSEKITARAN DI KELANTAN

Latar belakang: Jangkitan malaria *P. knowlesi* telah muncul di Kelantan sejak dua dekad lalu. Walaupun terdapat banyak langkah pencegahan untuk mengawal jangkitan malaria *P. knowlesi*, namun arah aliran jangkitan di Kelantan tidak diramalkan akan berkurangan dalam masa terdekat. Bagi menambah baik langkah kawalan jangkitan malaria *P. knowlesi* di Kelantan, penilaian hubungan antara malaria *P. knowlesi* dan persekitaran adalah penting kerana kesan faktor persekitaran seperti reruang, iklim dan perubahan dalam penggunaan tanah mempunyai kesan terhadap penularan dinamik malaria *P. knowlesi*. Oleh itu, kajian ini bertujuan untuk memetakan kepadatan reruang bagi kes malaria *P. knowlesi* di Kelantan secara kumulatif dan tahunan, untuk mengkaji hubungan antara penunjuk meteorologi dan risiko relatif malaria *P. knowlesi* di Kelantan menggunakan model lag terdistribusi tak linear, dan untuk meramalkan taburan geografi insiden malaria *P. knowlesi* menggunakan data daripada sistem e-Vekpro dari tahun 2012 hingga tahun 2021 di Kelantan, Malaysia. **Kaedah:** Kajian ini dijalankan menggunakan semakan data sekunder ke atas kes malaria yang berdaftar dalam sistem e-Vekpro dari 2012 hingga 2021 melalui perisian R. Peta kepadatan reruang bagi kes malaria *P. knowlesi* itu distratifikasikan mengikut kumpulan umur, jantina, bulan, dan tahun diagnosis, dan diramalkan menggunakan anggaran ketumpatan kernel melalui pakej 'spatstat'. Enam pembolehubah meteorologi dari Stesen Cuaca Kuala Krai iaitu bacaan jumlah hujan harian, purata suhu harian, suhu minimum harian, suhu maksimum harian, purata kelajuan angin permukaan harian dan purata kelembapan relatif harian diperoleh daripada Jabatan Meteorologi Malaysia. Model lag terdistribusi tak linear telah digunakan untuk mengkaji parameter meteorologi berkorelasi yang signifikan terhadap risiko relatif jangkitan malaria *P. knowlesi* di Kelantan. Kaedah model Bayesian geostatistik berdasarkan penganggaran Laplace bersepadu tersarang dan pendekatan persamaan pembezaan separa stokastik digunakan untuk memetakan ramalan insiden malaria *P. knowlesi* di Kelantan dengan resolusi reruang 5 x 5 kilometer. Pendekatan kaedah model geostatistik ini menggunakan data raster selanjar sebagai kovariat daripada pelbagai sumber terbuka, iaitu hujan, suhu purata, julat tahunan suhu, tekanan wap air, kelajuan angin, altitud, ketinggian hutan dan kepadatan penduduk, mewakili faktor persekitaran. **Keputusan:** Sebanyak 1014 kes telah dimasukkan dalam kajian ini. Pemetaan kepadatan reruang menunjukkan bahawa kawasan pedalaman Kelantan mempunyai kepadatan reruang yang lebih tinggi bagi jangkitan malaria *P. knowlesi*. Variasi kepadatan reruang menunjukkan kes dikalangan lelaki adalah lebih berterabur dan tersebar ke arah barat, timur dan selatan sempadan Kelantan. Kes berumur diantara 20 hingga 49 tahun lebih tertumpu di di daerah Gua Musang. Sementara itu, kes dikalangan kumpulan umur yang lain adalah lebih berkelompok di daerah Jeli, Kuala Krai dan Gua Musang. Variasi masa mengikut bulan menunjukkan kes lebih tertumpu di daerah Jeli, Kuala Krai dan Gua Musang dari bulan Oktober hinggan April, kemudian daerah Jeli pada bulan Mi, dan daerah Gua Musang dari bulan Jun hingga September. Variasi masa mengikut tahun menunjukkan corak peralihan kepadatan reruang dari tengah Gua Musang ke arah selatan sempadan Kelantan. Hubungan antara pembolehubah meteorologi dan bilangan kes malaria *P. knowlesi* menunjukkan bahawa suhu minimum dan purata hujan mingguan dikaitkan secara signifikan dan berkadar songsang dengan bilangan kes malaria *P. knowlesi*. Purata hujan mingguan di bawah 4.2mm dikaitkan dengan risiko relatif lebih tinggi jangkitan malaria *P. knowlesi*, manakala purata hujan mingguan yang lebih tinggi daripada 4.2mm dikaitkan dengan risiko relatif lebih rendah jangkitan malaria *P. knowlesi* sehingga lag 12 minggu. Purata suhu minimum mingguan di bawah 23.4°C mengurangkan risiko relatif jangkitan malaria *P. knowlesi*, tetapi suhu melebihi 23.4°C meningkatkan risiko itu dalam tempoh lag 12 minggu. Analisa geostatistik menunjukkan reruang heterogeniti bagi ramalan taburan geografi insiden malaria *P. knowlesi* kelihatan jelas di bahagian barat tengah daerah Gua Musang dan merebak ke arah sempadan selatan Kelantan. Beberapa kawasan di Daerah Gua Musang telah diramalkan dengan insiden malaria *P. knowlesi* lebih tinggi daripada 450 kes bagi setiap 10000 penduduk, iaitu kira-kira 3.9 kali lebih tinggi daripada insiden yang diperhatikan. Insiden malaria *P. knowlesi* didapati berkadar terus dengan ketinggian pokok, purata suhu julat tahunan, kelajuan angin, dan tekanan wap air, dan berkadar songsang dengan ketinggian, purata suhu, dan hujan tahunan. Kebarangkalian dilampaui menunjukkan bahawa beberapa kawasan di daerah Gua Musang mempunyai risiko yang lebih tinggi untuk ramalan jangkitan malaria *P. knowlesi* melepasi 100 kes bagi setiap 10000 penduduk. **Kesimpulan:** Faktor persekitaran, termasuk meteorologi, topografi, dan litupan tanah memberi kesan kepada risiko relatif dan insiden malaria *P. knowlesi* di Kelantan. Ini boleh memberikan maklumat tambahan bagi merancang intervensi yang lebih innovatif dan strategik, mengoptimakan pengurusan kewangan dan tenaga manusia serta pendekatan multisektoral dalam pencegahan dan kawalan penyakit malaria *P. Knowlesi* di Kelantan khususnya.

Kata kunci: malaria *P. knowlesi*, Kelantan, kepadatan reruang, model lag bukan linear terdistribusi, penganggaran Laplace bersepadu tersarang.

ABSTRACT

THE RELATIONSHIP BETWEEN *PLASMODIUM KNOWLESI* MALARIA DISTRIBUTION AND ENVIRONMENTAL FACTORS IN KELANTAN

Introduction: *P. knowlesi* malaria infection has emerged in Kelantan for the past two decades. Despite considerable preventive measures to combat *P. knowlesi* malaria infection, the prevalence of *P. knowlesi* malaria in Kelantan is not predicted to decline anytime soon. To improve control measures of *P. knowlesi* malaria infection in Kelantan, the assessment of the relationship between *P. knowlesi* malaria and the environment is important due to the impact of environmental factors, such as spatial, climatic, and land use changes, on the transmission dynamics of *P. knowlesi* malaria. Thus, this study aimed to develop the cumulative and annual spatial intensity map of notified *P. knowlesi* malaria infection in Kelantan, to estimate the relationship between meteorological indicators and the relative risk of *P. knowlesi* malaria in Kelantan using distributed lag non-linear analysis, and to predict the geographical distribution of *P. knowlesi* malaria incidence using data from e-Vekpro system from the year 2012 to year 2021 in Kelantan, Malaysia. **Methods:** The secondary data review was conducted using registered malaria cases in the e-Vekpro system from 2012 to 2021 via R software. The spatial intensity map of the cases was stratified by age group, sex, month, and year of diagnosis, and was estimated using kernel density estimation via 'spatstat' package. Six meteorological variables from Kuala Krai Weather Station, namely daily rainfall, daily mean temperature, daily minimum temperature, daily maximum temperature, daily mean surface wind speed and daily mean relative humidity were obtained from Malaysia Meteorological Department. A distributed lag non-linear model was used to examine the significant correlated meteorological parameters on the relative risk of *P. knowlesi* malaria infection in Kelantan. Bayesian geostatistical modeling based on integrated nested Laplace approximation and stochastic partial differential equation approach was used to map the predicted *P. knowlesi* malaria incidence in Kelantan with a 5 x 5 kilometers spatial resolution. This geostatistical approach used open-source continuous raster data as covariates from various sources, namely rainfall, mean temperature, temperature annual range, water vapor pressure, wind speed, elevation, forest height, and population density, representing environmental factors. **Results:** A total of 1014 cases were included in the study. Mapping of spatial intensity demonstrated that the interior area of Kelantan had a higher spatial intensity of *P. knowlesi* malaria infection. Spatial variation of case intensity demonstrated that cases among male were more scattered and dispersed towards Kelantan's western, southern, and eastern border. The cases aged between 20 to 49 years old were more abundant within Gua Musang district. Meanwhile, the other age groups tend to be clustered in Jeli and Kuala Krai districts. Temporal variation by month revealed that the cases become more abundant in Jeli, Kuala Krai, and Gua Musang districts from October to April, then Jeli districts in May, and Gua Musang districts from June to September. Temporal variation by year showed a shifting pattern of case intensity from center of Gua Musang towards the southern Kelantan border. The relationship between a meteorological variable and the number of *P. knowlesi* malaria cases reveals that the minimum temperature and weekly average rainfall were significantly and negatively associated with the number of *P. knowlesi* malaria cases. Weekly average rainfall below 4.2mm was linked to a higher relative risk of *P. knowlesi* malaria, while higher than 4.2mm was linked to a lower relative risk of *P. knowlesi* malaria up to 12 lag weeks. Weekly average minimum temperatures below 23.4°C reduce the relative risk of *P. knowlesi* malaria, but temperatures over 23.4°C raise that risk within 12 lag weeks. Geostatistical analysis shows spatial heterogeneity of predicted geographical distribution of *P. knowlesi* malaria infection was prominent over the central western part of the Gua Musang district and spread toward the southern border of Kelantan. Several areas in Gua Musang District have predicted geographical incidence of *P. knowlesi* malaria higher than 450 cases per 10000 population, which is approximately 3.9 times higher than the observed incidence. The exceedance probability suggested that several areas in the Gua Musang district have a higher chance of predicted *P. knowlesi* malaria infection than 100 cases per 10000 population. **Conclusion:** Environmental factors, including meteorology, topography, and land cover, have an impact on the relative risk and incidence of *P. knowlesi* malaria in Kelantan. This may provide additional information for a more innovative and strategic intervention planning, optimizing funding allocation and human resources, as well as multisectoral approach in *P. knowlesi* malaria prevention and control specifically in Kelantan.

Keywords: *P. knowlesi* malaria, Kelantan, spatial intensity, Distributed lag non-linear, Integrated nested Laplace approximation.

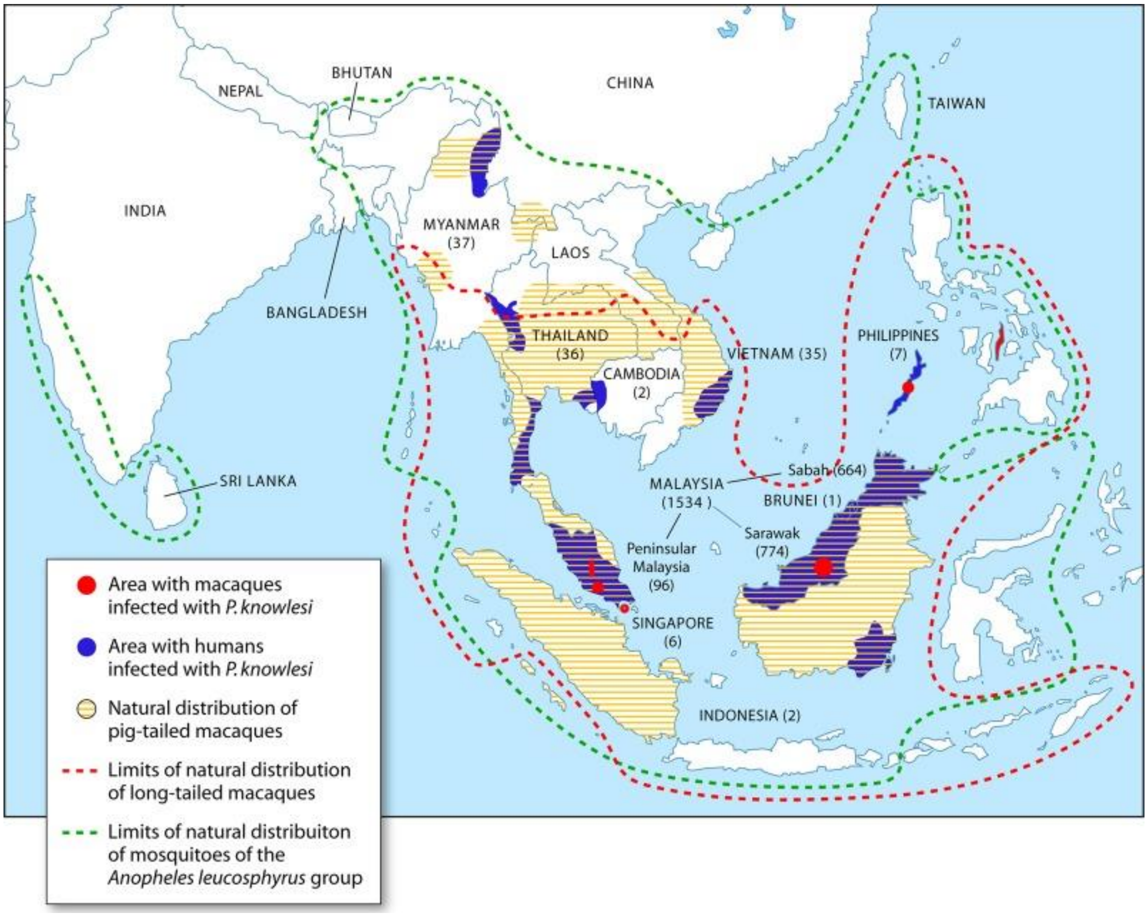
CHAPTER 1: INTRODUCTION

1.1 Background of *P. knowlesi* Malaria

Plasmodium knowlesi (*P. knowlesi*) malaria is an emerging disease that is endemic in Malaysia and has been reported in other Southeast Asia countries. *P. knowlesi* malaria is classified as zoonotic malaria, unlike the other established four species of human malaria, which are considered true parasites to humans; *Plasmodium falciparum* (*P.falciparum*), *Plasmodium malariae* (*P. malariae*), *Plasmodium vivax* (*P. vivax*) and *Plasmodium ovale* (*P. ovale*). However, some literature has used simian malaria in humans as an interchangeable term with zoonotic malaria due to the transmission of the malaria parasite from macaques to humans via mosquitoes.

In the epidemiological triad, the transmission of *P. knowlesi* malaria infection in humans involved the three main factors; the human as the host, the parasite as the agent and the environment which in this infection include simian host and its habitat, and another factor which is the mosquitoe as the vector (Chin *et al.*, 2020a). Simian hosts such as wild long-tailed macaque (*Macaca fascicularis*), pig-tailed macaques (*Macaca nemestrina*), and banded leaf monkeys (*Presbytis malalophus*) were easily found exclusively in Southeast Asia. However, many were infected with the *P. knowlesi* malaria parasite (Lee *et al.*, 2011). This factor is the crucial reason why *P. knowlesi* malaria infection was concentrated and became a primary issue in the Southeast Asia region only. The vector of *P. knowlesi* malaria is predominantly *Anopheles leucosphyrus* group mosquitoes. Still, other remaining group of Anopheles mosquitoes, such as the *Anopheles barbirostris* group and the *Anopheles umbrosus* group, has limited evidence in transmitting *P. knowlesi* malaria from simian host to human. Remarkably, the distribution of *Anopheles leucosphyrus* group mosquitoes is closely matched with the distribution of long-tailed monkeys, which increases the risk of *P. knowlesi* malaria transmission in Southeast Asia (van de Straat *et al.*, 2022). Deforestation and other types of land use changes, such as agricultural expansion and forest fragmentation, were significant environmental factors that increased the risk of *P. knowlesi* malaria transmission (Fornace *et al.*, 2016; Fornace *et al.*, 2019; Moyes *et al.*, 2016). Figure 1.1 shows the distribution of *P. knowlesi* malaria cases among humans and macaques by regions or countries as described by Singh and Daneshvar (2013), with the natural distribution of pig-tailed macaques, long-tailed macaques, and *Anopheles leucophyrus* mosquitoes. To conclude this elaboration, any human who engages in activities that reside in or travel through a high-risk area where monkeys and mosquitoes cohabit will be at a higher risk of contracting *P. knowlesi* malaria.

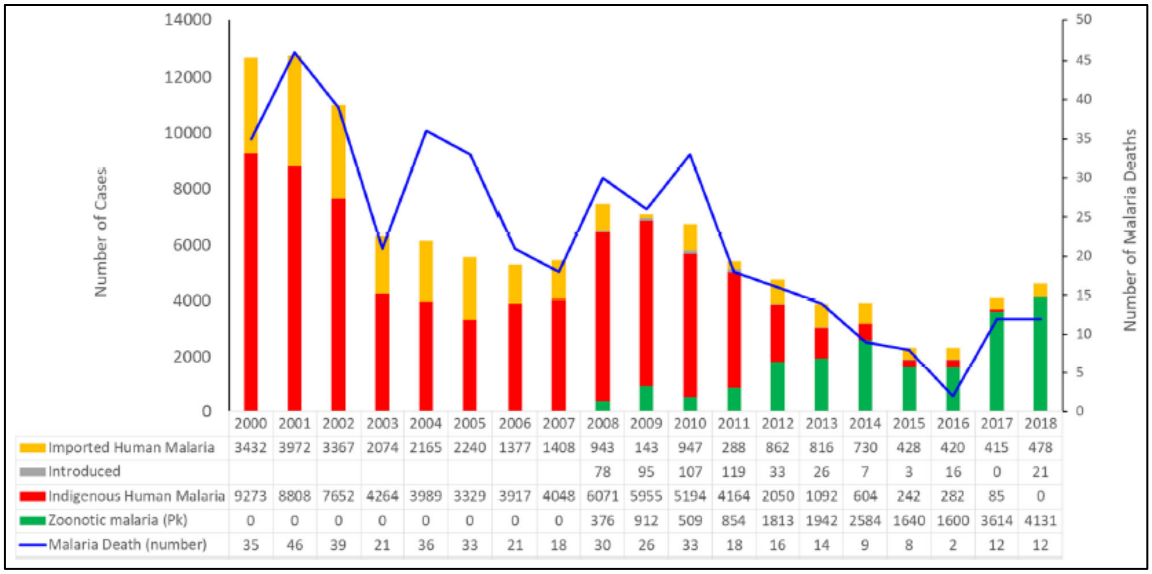
Due to the complexity of the epidemiological triad *of P. knowlesi* malaria infection, this disease poses many challenges to curbing the disease transmission in the last two decades. Therefore, the World Health Organisation (WHO) has introduced several terminologies to determine the source of malaria infection, such as indigenous, introduced, and imported cases (World Health Organization, 2021). These terms are commonly used in the prevention and control of malaria and are used to track the origin of the malaria infection, and therefore the transmission of malaria infection can be disrupted. The imported case is the case which is obtaining malaria infection outside the area where the diagnosis of malaria was made. The introduced case is the case who are contracting malaria locally from an imported case with the presence of strong epidemiological evidence. Meanwhile, the indigenous case is the case that is obtaining malaria infection without evidence of importation or transmission from imported cases. Thus, due to the cohabitation of simian hosts and Anopheles mosquitoes in Malaysia, it is common to encounter *P. knowlesi* malaria outbreaks among human with indigenous in nature.



Error! Reference source not found.: Area with humans and macaques infected with *P. knowlesi* malaria and natural distribution of macaques and *Anopheles leucophyrus* mosquito (Singh and Daneshvar, 2013).

Malaysia has established zero indigenous human malaria transmission since 2018, targeting a malaria-free country soon. The World Health Organization has identified

Malaysia as one of the 21 malaria-eliminating countries under E-2020 initiatives that could achieve zero indigenous human malaria cases by 2020 (World Health Organization, 2019). In 2018, all imported, introduced, and indigenous human malaria infections decreased dramatically, with no indigenous human malaria reported in Malaysia ((Chin *et al.*, 2020b); Figure 1.2)



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
🟨 Imported Human Malaria	3432	3972	3367	2074	2165	2240	1377	1408	943	143	947	288	862	816	730	428	420	415	478
▬ Introduced									78	95	107	119	33	26	7	3	16	0	21
🟥 Indigenous Human Malaria	9273	8808	7652	4264	3989	3329	3917	4048	6071	5955	5194	4164	2050	1092	604	242	282	85	0
🟩 Zoonotic malaria (Pk)	0	0	0	0	0	0	0	0	376	912	509	854	1813	1942	2584	1640	1600	3614	4131
— Malaria Death (number)	35	46	39	21	36	33	21	18	30	26	33	18	16	14	9	8	2	12	12

Figure 1.2: Trend of indigenous, introduced, imported, and zoonotic malaria infection in Malaysia from 2000 to 2018 (Chin *et al.*, 2020b).

Despite the effectiveness of public health actions demonstrated by the Ministry of Health of Malaysia in reducing human malaria cases, the emergence of *P. knowlesi* malaria infection in Malaysia does not reflect the effectiveness of those efforts and control measures in preventing *P. knowlesi* malaria transmission. The number of *P. knowlesi* malaria infections, zoonotic malaria, has increased steadily since 2008. This may be contributed by the establishment of polymerase chain reaction (PCR) test for *P. knowlesi* malaria. Prior to the implementation of the PCR test, *P. knowlesi* malaria was underdiagnosed due to the lack of a specific test for the *P. knowlesi* parasite, and it had been mistaken with another form of human malaria using blood films for malaria parasites (BFMP), such as *P. falciparum* during early blood-stage of the parasite and *P. malariae* during late blood-stage of the parasite (Huber *et al.*, 2023). *P. knowlesi* malaria were included in the list of Malaysia's notifiable disease in 2010 to monitor the trend of infection as it remained a significant health issue in Malaysia (Cuenca *et al.*, 2021).

The trend of *P. knowlesi* malaria infection in Kelantan was supposed to be reduced similar with the reduction of human malaria cases following the current national malaria strategic plan as it involves vector control as well. However, the proportion of *P. knowlesi* malaria in Kelantan is still high, and the cases showed an increment in trend (Phang *et al.*, 2020), which requires critical knowledge on innovative and effective implementation of numerous strategies and measures, current control, and preventive measures to combat *P. knowlesi* malaria infection in the future. One of the strategies to reduce *P. knowlesi* malaria occurrence is through the understanding of the disease distribution, with disease mapping models frequently used to visualize and estimate the distribution of the disease (Blangiardo et al., 2020). Thus, by understanding the spatial pattern and estimation of the geographical distribution of *P. knowlesi* malaria infection, it is helpful to improve current knowledge, case detection, intervention program, and resource allocation to control disease transmission in Kelantan in the future.

1.2 Spatial Analysis in Communicable Diseases Epidemiology

Spatial analysis is the process of examining the relationship between the spatial positioning of objects, phenomenon, and their characteristics (Loonis and de Bellefon, 2018). Meanwhile, spatiotemporal analysis is the process of identifying spatial variations of spatial data through time. In health, spatial epidemiology studies spatial variation in disease risk or occurrence (Ostfeld *et al.*, 2005). This study involves a wide range of techniques, and choosing appropriate spatial tools and presentation can be challenging. John Snow developed the first spatial epidemiology framework to predict the spatial distribution of cholera cases concerning possible risk factors in London in 1854 (Pfeiffer *et al.*, 2008).

Spatial and spatiotemporal data analysis is the emerging research technique that is used to represent the pattern of both communicable and non-communicable diseases using spatial and/or time data. The analysis requires health data that incorporates together with a geographic information system (GIS), a computer-based system, to anticipate the distribution of the disease and health outcome. This data analysis technique supplies better data visualization on spatial and temporal correlations, provides more dynamic information, determines the clustering effect of the diseases, and relates it to environmental risk, and allows the detection of persistent and uncommon patterns (Byun et al., 2021).

Vector-borne diseases and zoonoses are part of the infectious diseases that are dependent on climates and environmental factors, and almost all of these factors can be classified as spatial data. For instance, a recent systematic review showed that *P. knowlesi* malaria is strongly associated with ecological changes such as deforestation and land use change, mainly for agricultural activities. Besides, climates also play an essential role in the transmission of *P. knowlesi* malaria. For example, rainfall is associated with increased *P. knowlesi* malaria infections, and seasonal variation also influences the number of *P. knowlesi* malaria infections in Sabah (Steven *et al.*, 2020). Therefore, these environmental findings could be included in the spatial and spatiotemporal analysis of *P. knowlesi* malaria infection to benefit public health intervention and policy makers in the future.

1.3 Problem Statement

Malaysia has a long history of combating malaria transmission, starting with Malaria Eradication Program in 1961 in East Malaysia and 1967 in Peninsular Malaysia, followed by the National Malaria Elimination Strategic Plan 2010-2020 (Chin *et al.*, 2020a). Recently, World Malaria Report 2022 reported that Malaysia had zero indigenous human malaria cases for four consecutive years, but *P. knowlesi* malaria cases have been prominent in the past five years. The recently re-emerged *P. knowlesi* malaria was mainly due to the challenges in controlling the monkey parasite reservoir (Benavente et al., 2019; Chin et al., 2020).

The incidence of *P. knowlesi* malaria infection was higher in East Malaysia, thus, many studies to understand the distribution and determinants of *P. knowlesi* malaria were carried out within this region. In Peninsular Malaysia, Kelantan State had the highest number of *P. knowlesi* malaria cases (Phang *et al.*, 2020). Unlike East Malaysia, fewer studies were conducted to understand *P. knowlesi* malaria infection in Peninsular Malaysia, especially

Kelantan State. Thus, these reasons imply that the need for knowledge updates on *P. knowlesi* malaria infection in Kelantan is required to improve strategies to control *P. knowlesi* malaria transmission in the future.

Malaysia still has limited up-to-date spatial data that represent the epidemiology of *P. knowlesi* malaria. The latest spatial and temporal study in Malaysia was carried out by Phang *et al.* (2020), which describes the distribution and trend of *P. knowlesi* malaria in West Malaysia using areal data, spatial autocorrelation, and the SARIMA model. Previous advanced spatial analysis was used by Moyes *et al.* (2016) to describe the predicted spatial distribution of simian hosts and Anopheles mosquitoes of *P. knowlesi* malaria in Southeast Asia using boosted regression tree method. All the studies mention the limitation of optimal measures for controlling and preventing *P. knowlesi* malaria. The understanding of the dynamics and epidemiology of *P. knowlesi* malaria in Malaysia is still limited using spatial analysis.

1.4 Rationale of the Study

Spatiotemporal analysis on *P. knowlesi* malaria play a crucial role in disease prevention and control, as it provides valuable insights into the pattern of disease spread and identifies high-risk areas to guide more targeted interventions. The study to evaluate the distribution and temporality of *P. knowlesi* malaria infections in Kelantan is limited, as the study was extensively conducted in Sabah and Sarawak due to the high incidence of *P. knowlesi* malaria in this region (Hussin et al., 2020). Although Kelantan has a lower *P. knowlesi* malaria incidence compared to East Malaysia, the findings from the study in East Malaysia are still implying a similar risk to the health of vulnerable communities and targeted groups, even in the Kelantan region. Thus, this study is beneficial and essential to update the current knowledge of the distribution and temporality of *P. knowlesi* malaria infection in Kelantan.

There is a need to know more about the epidemiology of *P. knowlesi* malaria infection in Kelantan. The vector, simian host, parasites for *P. knowlesi* malaria, and the nature of human activities in Kelantan is slightly differed from those in East Malaysian, indicating a different *P. knowlesi* malaria transmission risk to the human population between these two regions. In general, the epidemiology of *P. knowlesi* malaria in West Malaysia region involved different *Anopheles leucosphyrus* groups of mosquito species and the genetic population of *P. knowlesi* malaria parasites (Benavente *et al.*, 2019), leads to variation in transmission rate of *P. knowlesi* malaria to human. Simian hosts in Peninsular Malaysia also showed slightly different macaque species, with a lower proportion of infected simian hosts than the simian host in East Malaysia (Sam *et al.*, 2022; Singh and Daneshvar, 2013). The different nature of human activities in high-risk areas also contributed to the lower transmission risk of *P. knowlesi* malaria in Peninsular Malaysia.

The primary focus of the study is assessing the distribution of *P. knowlesi* malaria infection in Kelantan states, as almost thirty percent of *P. knowlesi* malaria cases notified in the Peninsular Malaysia region originated from Kelantan (Phang et al., 2020). Therefore, this research's scope may emphasize the relationship between environmental factors and the incidence of *P. knowlesi* malaria in Kelantan.

1.5 Research Questions

1. What is the spatial intensity of *P. knowlesi* malaria infections in Kelantan?
2. How do the meteorological indicators influence the risk of *P. knowlesi* malaria in Kelantan?
3. What is the predicted geographical distribution of *P. knowlesi* malaria incidence in Kelantan?

1.6 Objectives

1.6.1 General objective

To examine the trend of *P. knowlesi* malaria and the relationship between *P. knowlesi* malaria and environmental factors in Kelantan, Malaysia using data from e-Vekpro system from the year 2012 to the year 2021.

1.6.2 Specific objectives

1. To map the cumulative and annual spatial intensity of notified *P. knowlesi* malaria infection in Kelantan, Malaysia from the year 2012 until the year 2021.
2. To estimate the relationship between meteorological indicators and the relative risk of *P. knowlesi* malaria in Kelantan, Malaysia using distributed lag non-linear analysis.
3. To predict the geographical distribution of *P. knowlesi* malaria incidence from the year 2012 to the year 2021 in Kelantan, Malaysia.

1.7 Research Hypothesis

1. There is a significant relationship between meteorological variation and the risk of *P. knowlesi* malaria infection in Kelantan.
2. There is a significant variation in the geographical distribution of *P. knowlesi* malaria incidence from the year 2012 to year 2021 in Kelantan.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of *P. knowlesi* malaria

P. *knowlesi* malaria infection has been reported to be increased in Malaysia and other countries in Southeast Asia. In Malaysia, Hussin et al. (2020) reported that the annual incidence rate of *P*. *knowlesi* malaria infection per 1000 population in Malaysia was between 0.073 to 0.128 between the year 2013 to 2017. However, the incidence rate of this infectious disease was higher in Sabah and Sarawak compared to Peninsular Malaysia, where Sabah and Sarawak have reported an annual incidence rate of 0.268 to 0.512 per 1000 population while Peninsular Malaysia reported an annual incidence rate of 0.016 to 0.052 per 1000 population in a similar timeframe.

The proportion of *P*. *knowlesi* malaria infection in Malaysia among all malaria cases ranged from 9.9% to 98.0% (Chin et al., 2021; Cooper et al., 2019; Pramasivan et al., 2021; Yusof et al., 2014). In other countries in Southeast Asia, the prevalence of *P*. *knowlesi* malaria infection ranged between 0.3% to 46.5% among all types of malaria infection, a lower proportion compared to Malaysia (Herdiana et al., 2016; Jiang et al., 2010; Khim et al., 2011; Putaporntip et al., 2009; Sugaram et al., 2021). The increments in the incidence of *P*. *knowlesi* malaria cases are contributed by improved diagnostic capacity, reduction of relative immunity to malaria following decreased in human malaria, living, or working in the area confined to the natural distribution of simian host and vectors of *P*. *knowlesi* malaria. Besides, the improvement of knowledge and awareness of *P*.

knowlesi malaria infection among the population at risk also contributed to the increment of disease screening and case detection (Amir et al., 2018).

Severe disease of *P. knowlesi* malaria infection in Malaysia occurred in six to nine percent of total *P. knowlesi* malaria cases (Benavente et al., 2019). Meanwhile, the annual case fatality rate among people who are notified of *P. knowlesi* malaria in Sabah, Malaysia, was between 1.08 to 9.17 per 1000 case notifications (Rajahram et al., 2016). In Southeast Asia countries other than Malaysia, the proportion of severe *P. knowlesi* malaria cases and case fatality rate may be inaccurate due to limited sampling (World Health Organization, 2017). However, a study by Shearer et al. (2016) has predicted that Cambodia, Thailand, Vietnam, Myanmar, Indonesia, Philippines, and Laos may have a higher risk of getting *P. knowlesi* malaria infection, similar to Malaysia.

2.2 Spatial and Spatiotemporal Studies on *P. knowlesi* Malaria

2.2.1 Spatial and spatiotemporal studies of *P. knowlesi* malaria in Southeast Asia

Spatial analysis has been used to describe the distribution and the risk of *P. knowlesi* malaria infection. On the other hand, the spatiotemporal analysis describes the spatial and trend of disease distribution. During the discovery of a significant focus of *P. knowlesi* malaria infection in Southeast Asia in early 2000, Cox-Singh and Singh (2008) described the spatial distribution of *P. knowlesi* malaria cases was significantly related to the natural distribution of both simian host and vectors, as in Figure 2.1. Cox-Singh and Singh (2008) noted that *P. knowlesi* malaria transmission occurs in the area where mosquitoes and simian hosts coexist. However, the transmission rate differs between regions in Southeast Asia despite their similar existence. Sarawak had shown the highest incidence rate of *P. knowlesi* malaria in Southeast Asia. Cox-Singh and Singh (2008) suggested that *P. knowlesi* malaria infection in Southeast Asia was underdiagnosed, and there was a chance of a high incidence rate of *P. knowlesi* malaria infection in Southeast Asia areas other than Sarawak.

Later, Moyes *et al.* (2014) mapped the area with the evidence of *P. knowlesi* malaria reservoir in Southeast Asia and neighbouring countries by sub nations as in Figure 2.2 using the schematic system based on previous literature. This study has enlightened the researcher to understand the spatial variability of *P. knowlesi* malaria risk to humans from the infectious reservoir. However, the author has addressed that the spatial variation produced by this study is not to determine the likelihood of a reservoir within a particular area in Southeast Asia. Panel A in Figure 2.2 showed strong evidence that *P. knowlesi* malaria reservoir was the area with confirmed human infection. Weak evidence represented reservoir potentially infectious to humans by *P. knowlesi* malaria parasites documented in *macaca* species regardless of the presence of mosquitoes. The absence or minimal evidence of infectious reservoir prerequisites represents the monkey without evidence of *P. knowlesi* malaria parasites, irrespective of the presence of the mosquito. This study gave a rough idea of the range of reservoirs of *P. knowlesi* malaria in Southeast Asia. It also provided the outputs for future spatial modelling of *P. knowlesi* malaria.

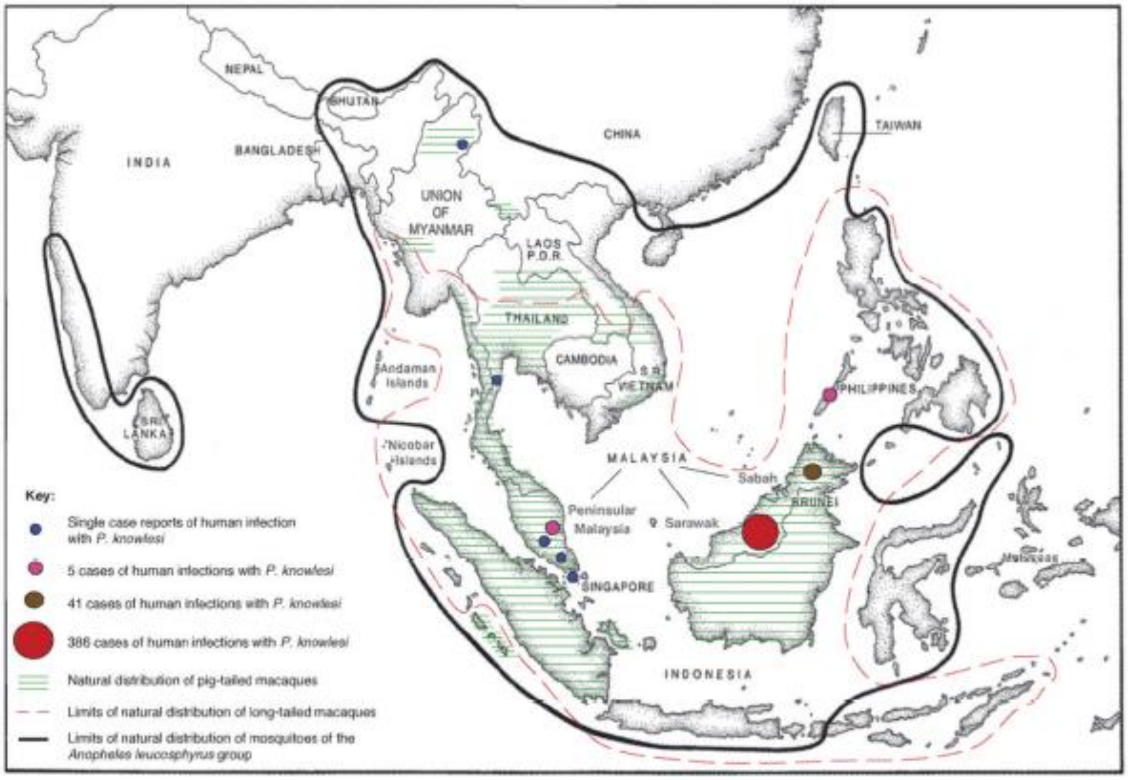


Figure 2.1: Distribution of reported human infections with *P. knowlesi* malaria and natural distribution of both simian host and mosquito of *Anopheles leucosphyrus* group (Cox-Singh and Singh, 2008).

Moyes *et al.* (2016) also extended the study through spatial modeling to predict the geographical distribution of macaca hosts (Panel A in Figure 2.3) and vectors of *P. knowlesi* malaria (Panel B in Figure 2.3) in Southeast Asia. The author used boosted regression tree method, the model commonly used in the previous analysis of the distribution of malaria vector species, to predict those outcomes. The predicted distribution of simian hosts and vectors was tested and modeled using several environmental and human population variables. The modeling helps identify the area with a higher risk of *P. knowlesi* malaria infection by overlapping the predicted

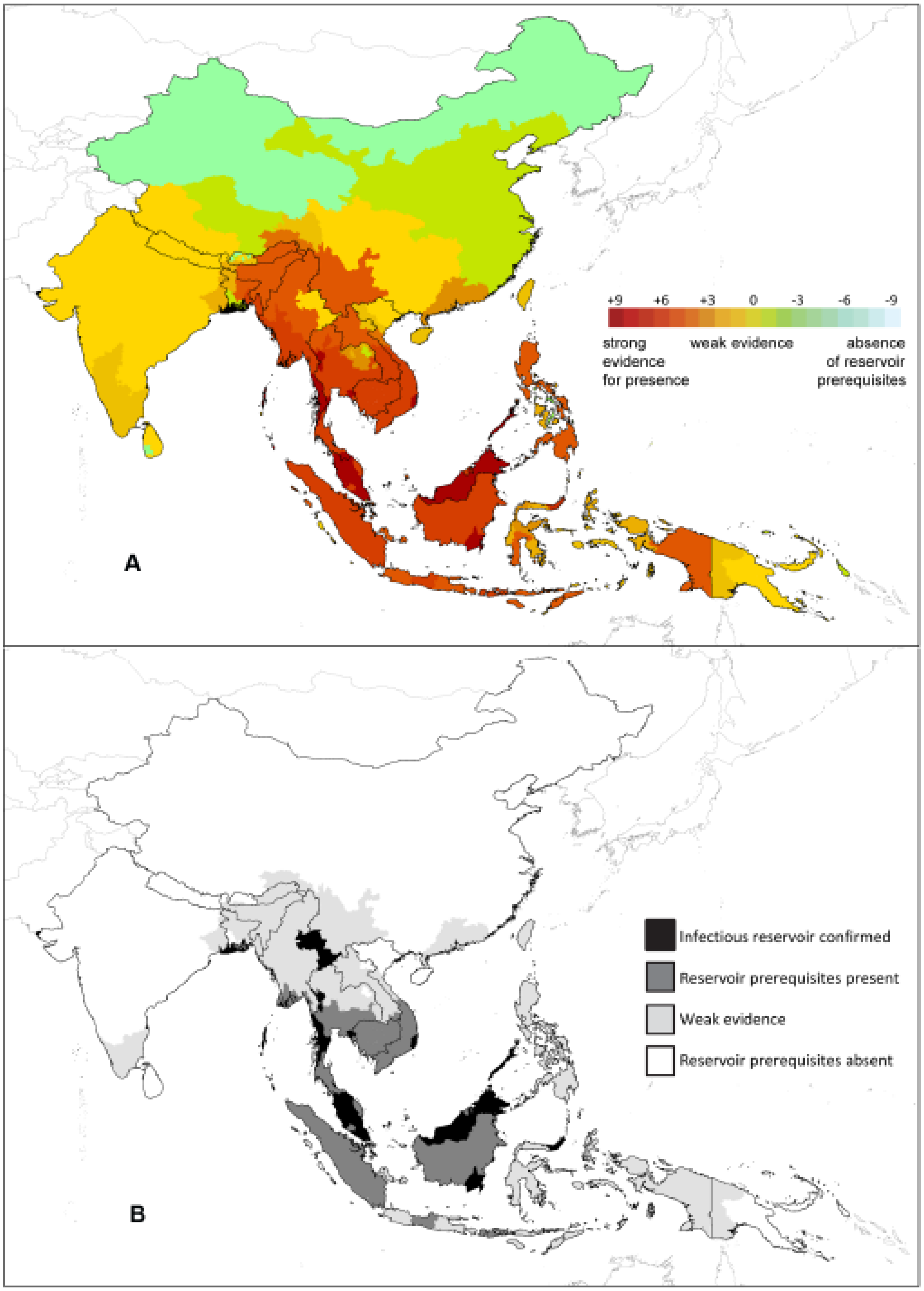


Figure 2.2: Evidence of *P. knowlesi* malaria using a schematic system to assign and rank the evidence score to each area. Panel A showed the evidence level of getting *P. knowlesi* malaria infection. Panel B showed similar evidence of *P. knowlesi* malaria infection as in Panel A, but the risk of *P. knowlesi* malaria infection was categorized into four groups (Moyes *et al.*, 2014).

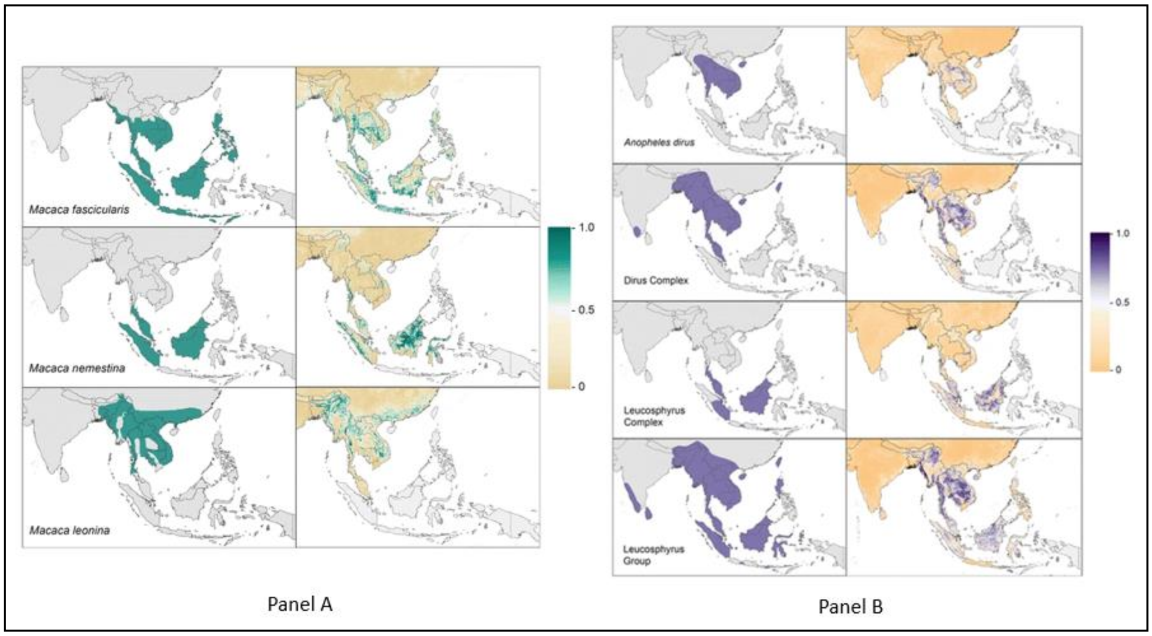


Figure 2.3: Range (right column) and predicted distribution (left column) of the *macaca* (Panel A) and mosquito species, complex and group (Panel B) (Moyes *et al.*, 2016).

geographical distribution of simian hosts and vectors. Moyes *et al.* (2016) suggested that the risk map of *P. knowlesi* malaria should be modelled using the distribution of simian hosts and vectors with geographical, environmental, and socioeconomic factors.

Shearer *et al.* (2016) have estimated the predicted spatial variation of the relative risk of *P. knowlesi* malaria infection, as shown in Figure 2.4. The method of spatial modelling for relative risk prediction for this study was similar to the approach conducted by Moyes *et al.* (2016). This spatial variation of *P. knowlesi* malaria risk is valuable in surveillance activities on *P. knowlesi* malaria infection based on region. In addition, it helps identify targeted groups within communities with a higher risk of *P. knowlesi* malaria infection related to their workplace, job type, and dwelling area.

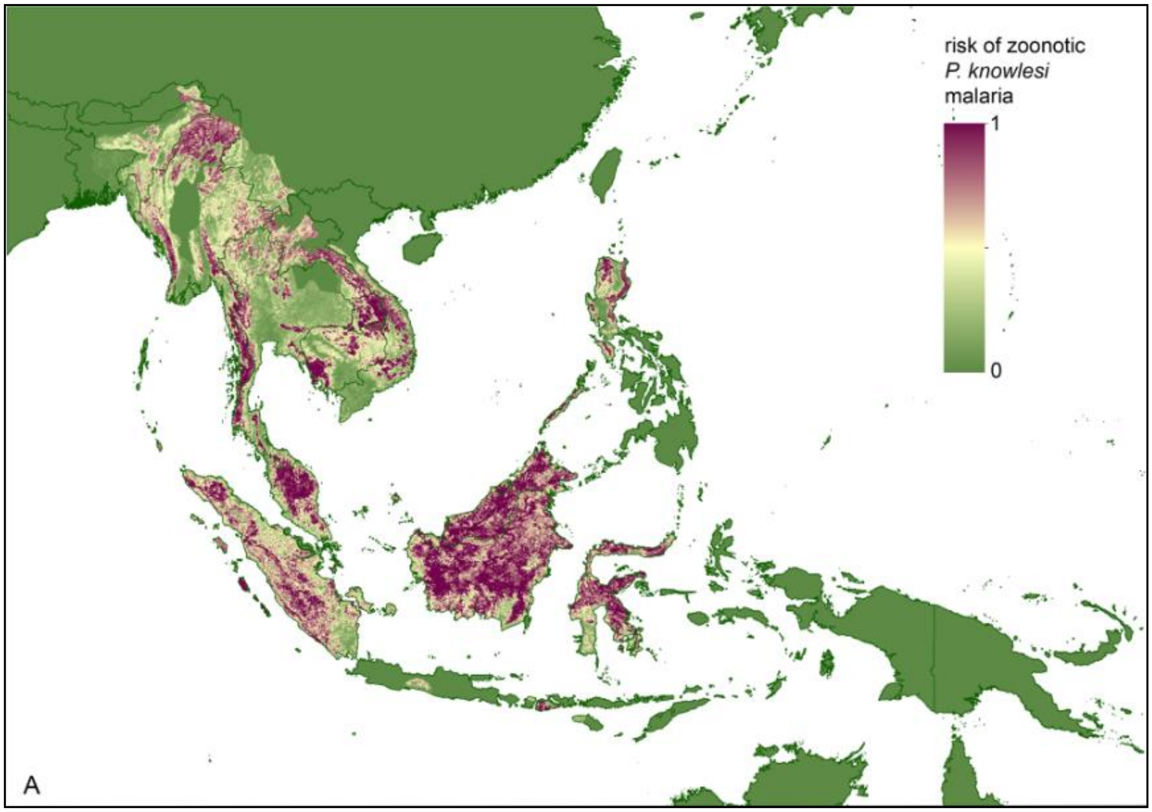


Figure 2.4: Predicted risk of *P. knowlesi* malaria infection in Southeast Asia (Shearer *et al.*, 2016).

2.2.2 Spatial and spatiotemporal studies of *P. knowlesi* malaria in Malaysia

Malaysia and other countries in Southeast Asia are well known for their high burden of *P. knowlesi* malaria infection due to abundant simian hosts and its vectors (Millar and Cox-Singh, 2015). Therefore, the pattern of spatial and spatiotemporal studies of *P. knowlesi* malaria infection has commonly been used on the distribution and occurrence of *P. knowlesi* malaria infection and its relationship to environmental factors. Recent studies have described the relationships between *P. knowlesi* malaria cases with land use changes, such as agricultural expansion and deforestation. Fornace *et al.* (2016) examined the association between landscape factors and spatial patterns of *P. knowlesi* malaria infection in Kudat and Kota Marudu, Sabah, between 2008 and 2012 using kernel density estimation methods. The study showed that the spatial distribution of the incidence of *P. knowlesi* malaria infection (Panel A in Figure 2.5) had similar spatial patterns from year to year, with some areas having persistent high incidence over time. Panel B in Figure 2.5 depicted forest coverage from 2008 to 2012, with a 4.8 percent reduction estimated using remote-sensing data. Even though this forest cover loss was stated to be highly localized in some areas, the author did not relate the spatial distribution of incidence of *P. knowlesi* malaria in Panel A with forest cover loss in Panel B.

Cooper et al. (2019) mapped the incidence rate of *P. knowlesi* malaria infection in Sabah by district and year from 2013 until 2017, as in Figure 2.6. The study reported that Keningau and Ranau district has the highest incidence rate throughout the study timeline. Similar to the finding by Fornace *et al.* (2016), the *P. knowlesi* malaria infection pattern showed a distinctive spatiotemporal pattern, with the incidence of *P. knowlesi* malaria infection being higher along the Crocker range.

A case-control study by Brock *et al.* (2019) used boosted regression tree analysis to predict the occurrence probability of P. knowlesi malaria infection in Kudat and Kota Marudu districts. The PCR-confirmed *P. knowlesi* malaria cases from 2012 until 2014 were compared to the non-malaria cases from the same village. The study reported that the likelihood of *P. knowlesi* malaria occurrence is high if the proportion of cleared land within one kilometre was low, as in Figure 2.7, suggesting that geolocation within forest patches and plantations has a higher risk of getting *P. knowlesi* malaria exposure. This

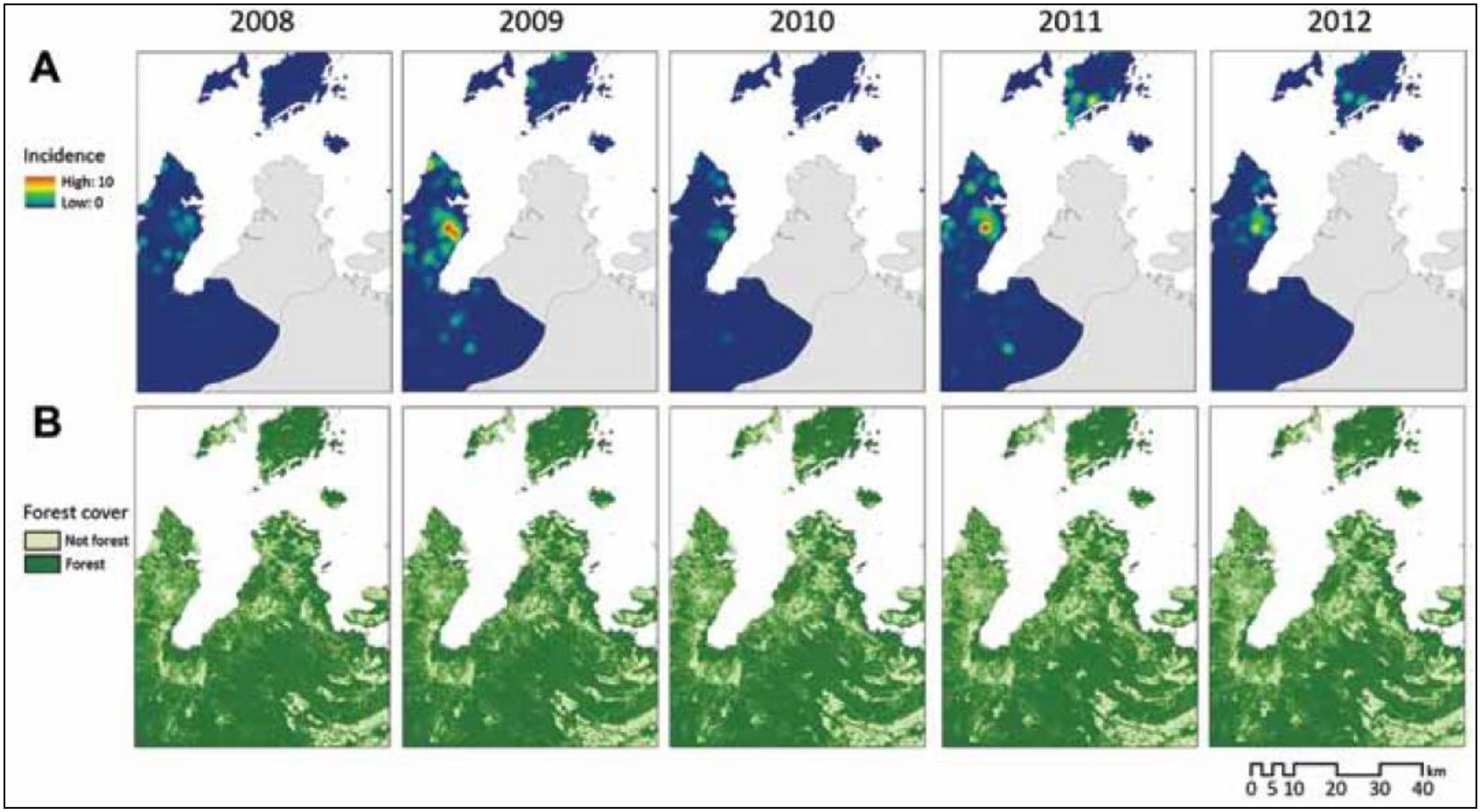


Figure 2.5: Comparison of estimated incidence of *P. knowlesi* malaria cases per 1000 population in relation to the forest cover in Kudat and Kota Marudu, Sabah (Panel A) and (Fornace *et al.*, 2016).

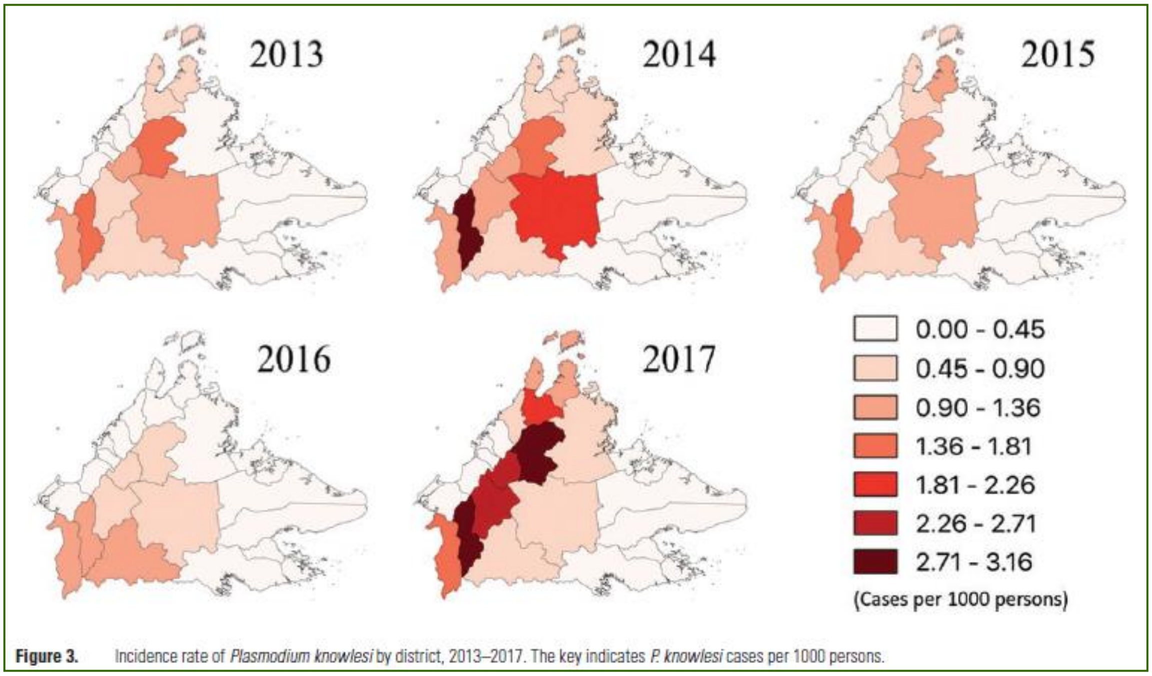


Figure 3. Incidence rate of *Plasmodium knowlesi* by district, 2013–2017. The key indicates *P. knowlesi* cases per 1000 persons.

Figure 2.6: The incidence rate of *P. knowlesi* malaria in Sabah from 2013 to 2017 by district (Cooper *et al.*, 2019).

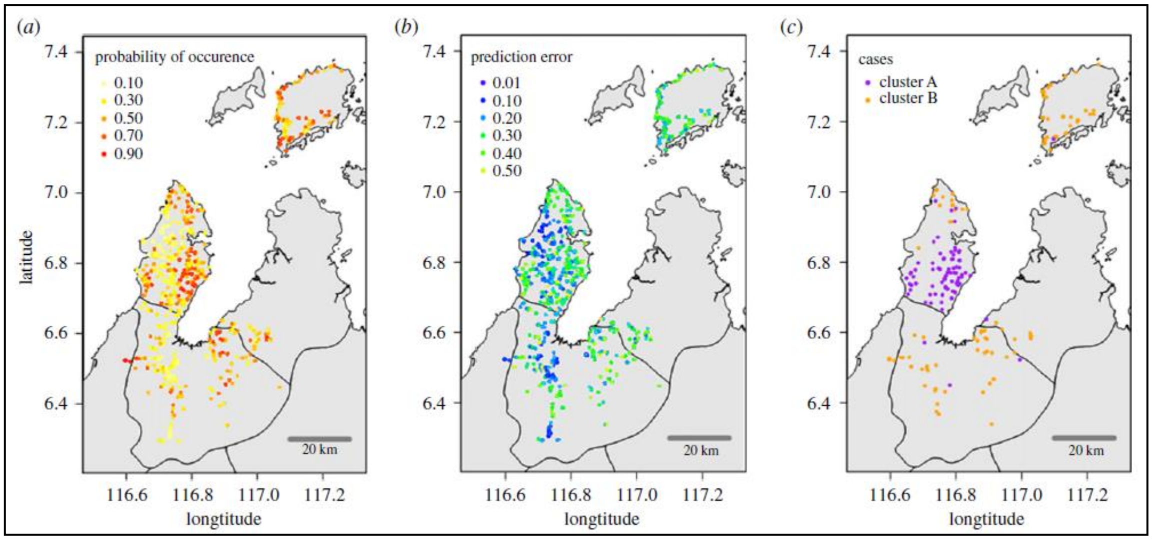


Figure 2.7: Predicted occurrence probability (a), prediction error (b), and two types of clusters of *P. knowlesi* malaria among case households using the case point and the spatial analysis by using boosted regression tree analysis (Brock *et al.*, 2019).

study also identified two types of case clustering based on spatial distribution patterns (Panel *c* in Figure 2.7). Cluster A had low forest cover, a relatively high proportion of cleared land, and a higher population density. Meanwhile, cluster B had fragmented forest cover in its surroundings. This clustering of cases showed that the cases in cluster A were more likely to obtain *P. knowlesi* malaria infection through travelling and other activities into the area with high risk of *P. knowlesi* malaria infection. Meanwhile, the cases in cluster B probably contracted the disease nearby their house through disease spillover, where the source of *P. knowlesi* malaria infection is from infected simian host that came into human settlement for food. However, this point pattern analysis did not provide density estimation for better data visualization and interpretation as it is challenging to differentiate multiple dots in an area with a high and low probability of *P. knowlesi* malaria infection risk.

A study on the predicted distribution of *P. knowlesi* malaria infection from 2011 to 2019 by Pramasivan *et al.* (2021) used the Kriging interpolation method to estimate hotspot area for targeted control strategies of *P. knowlesi* malaria infection in Johor. As in Figure 2.8, this study showed that hotspot regions of *P. knowlesi* overlapped or were close to the areas where *Anopheles. introlatus* and *Anopheles latens* were found. However, the author did not explain further the contributing environmental factors which may be valuable in preventing and controlling *P. knowlesi*. Phang *et al.* (2020) carried out a spatiotemporal study to determine the spatial pattern of the incidence rate of *P. knowlesi* malaria in Peninsular Malaysia from 2011 until 2018 using a choropleth map. Figure 2.9 shows that *P. knowlesi* malaria transmission was higher in the central region of Peninsular Malaysia, with the district of Gua Musang and Lipis constantly records a higher incidence

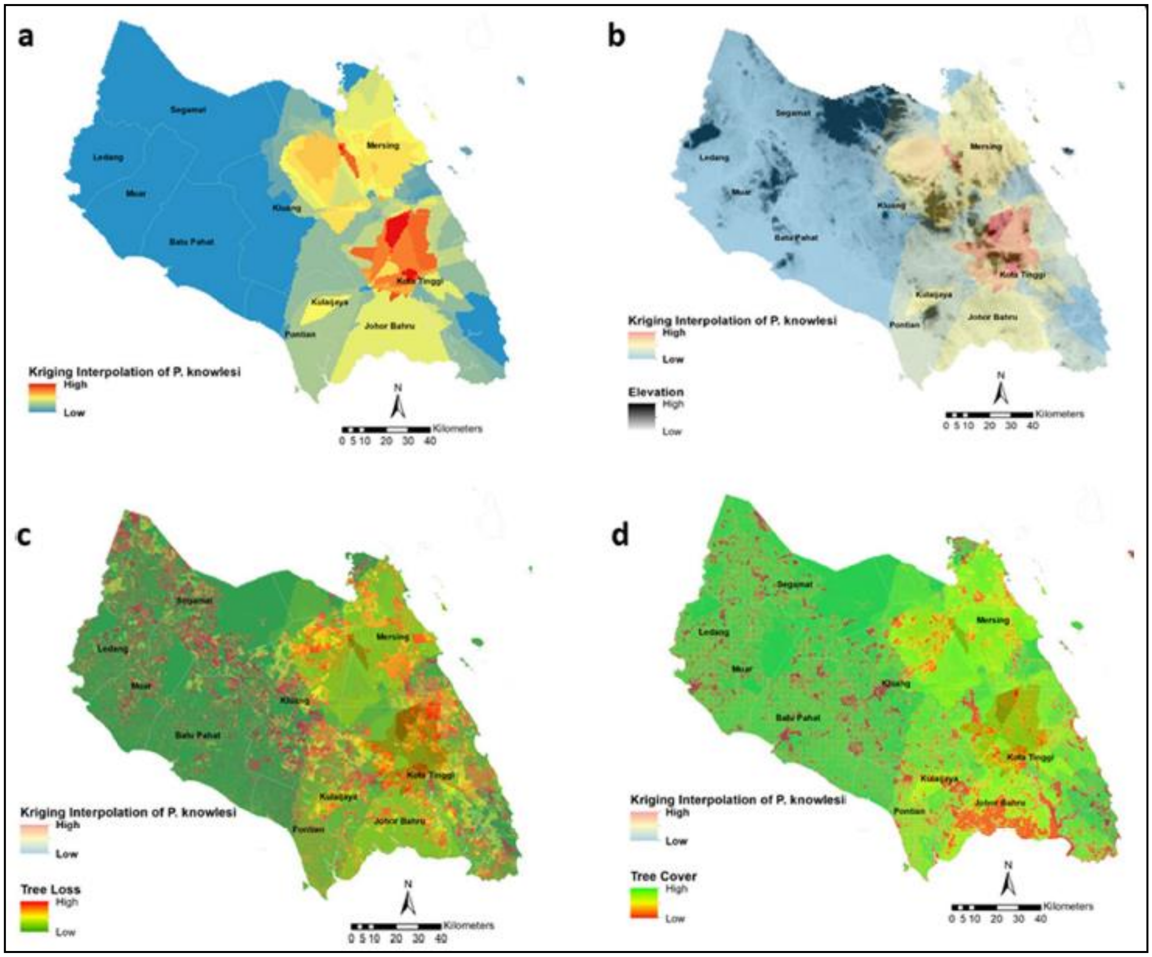


Figure 2.8: Spatial interpolation of distribution of *P. knowlesi* malaria infection in Johor (a), superimposed with elevation (b), tree loss (c), and tree cover (d).

Int. J. Environ. Res. Public Health **2020**, *17*, 9271 11 of 21

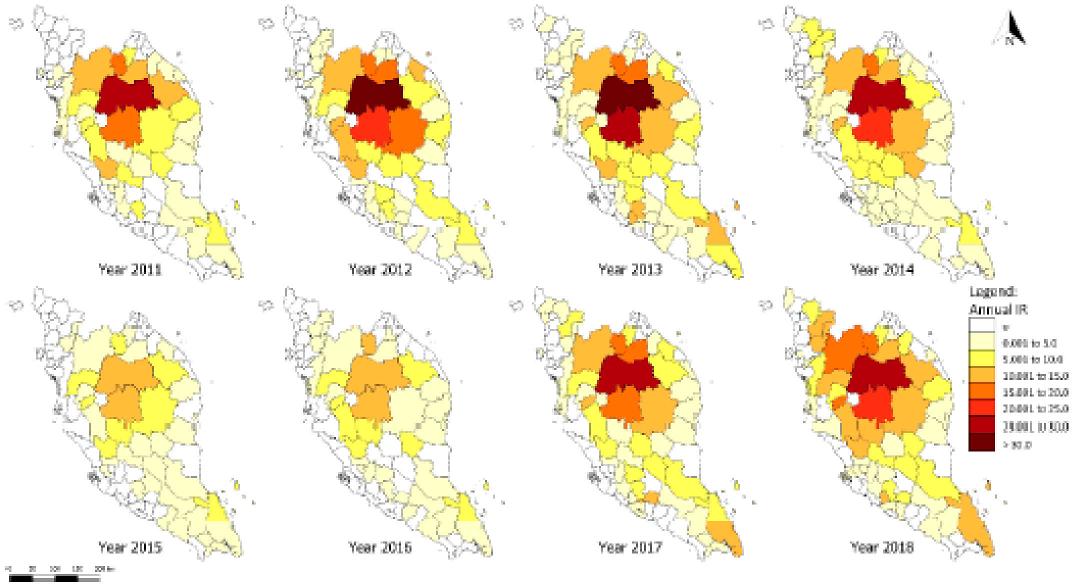


Figure 5. Spatial-temporal distribution of knowlesi malaria in Peninsular Malaysia (2011–2018).

Figure 2.9: Incidence rate of *P. knowlesi* malaria in Peninsular Malaysia by district and year (Phang *et al.*, 2020).

rate of *P. knowlesi* malaria annually. This is because these regions have large settlements of the aboriginal population, and their people have been frequently reported to be infected with *P. knowlesi* malaria infection. However, there was a transient drop in the incidence of *P. knowlesi* malaria infection in almost all districts in the year 2015 and 2016 compared with other years, possibly due to a reduction in case detection, a decline in vector density, and a decline in macaque population, or a reduction in human-mosquito interactions. The limitation of using a choropleth map in this study was the high annual incidence rates of *P. knowlesi* malaria districts are commonly located in route area. These districts are usually much bigger than the districts in the coastal area due to low population density, which give bias visual perception to the reader (Goovaerts, 2006).