INCIDENCE AND SPATIOTEMPORAL DISTRIBUTION OF PLASMODIUM KNOWLESI INFECTION IN PAHANG FROM 2011 TO 2022

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2023

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by

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Research Project Report submitted in partial fulfilment of the requirements for the degree of Master of Public Health

JUNE 2023

ACKNOWLEDGEMENTS

In the name of Allah, the Most Merciful and Most Compassionate. Salutations are extended to His Prophet Muhammad S.A.W, his family, and his companions. I would like to express my sincerest appreciation and gratitude to the subsequent individuals for their assistance and support in preparing this dissertation.

1. Associate Professor Dr. Nik Rosmawati Nik Husain, my supervisor, of whom has guided me throughout the research up to writing of this dissertation.
2. Dr. Ahmad Filza Ismail, my co-supervisor, who have supported me with the various analyses in this dissertation.
3. Dr. Suzana Binti Mohd Hashim, my co-researcher, who diligently provides information regarding *Plasmodium knowlesi* malaria data and assistance for this research.
4. All my lecturers from the Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, have guided and supported the course and dissertation.
5. My fellow colleagues from Master of Public Health.
6. My beloved wife, son, and daughter for their priceless support and motivation.
7. My dear parents and siblings, for the endless prayers.

Thank you for every word of encouragement and every second we spent together, which inspired me to stay motivated and complete this research project. May Allah bless you all for your patience and understanding on this incredible journey.

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LIST OF ABBREVIATIONS

BFMP	Blood Film for Malaria Parasite
DOSM	Department of Statistics Malaysia
e-Vekpro	Vekpro Online Database System
GIS	Geographical Information System
KDE	Kernel Density Estimation
LISA	Local Indicators of Spatial Association
MOH	Ministry of Heath
NNI	Nearest Neighbour Index
PCR	Polymerase Chain Reaction
SD	Standard Deviation
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

<	Less than
>	More than
=	Equal to
≤	Less than and equal to
≥	More than and equal to
%	Percentage

INSIDEN DAN TABURAN SPATIOTEMPORAL JANGKITAN PLASMODIUM KNOWLESI DI PAHANG DARI 2011 HINGGA 2022

ABSTRAK

Pengenalan: Malaria *Plasmodium knowlesi* merupakan masalah kesihatan awam yang penting di Pahang dan seluruh Malaysia. Ia boleh menyebabkan malaria parah dan membawa maut pada manusia, serta menimbulkan ancaman kepada usaha eliminasi malaria. Oleh itu, untuk penyediaan maklumat bagi mengenal pasti kawasan berisiko tinggi untuk membuat keputusan, dan peruntukan sumber yang membawa kepada kawalan dan strategi pencegahan yang lebih baik, maka analisis insiden serta analisis ruangan dan masa bagi malaria *P. knowlesi* perlu dilaksanakan.

Objektif: Untuk menilai kadar insiden dan taburan spatiotemporal jangkitan *P. knowlesi* di Pahang dari tahun 2011 hingga 2022.

Metodologi: Kajian hirisan lintang ini dijalankan dari Januari 2023 hingga Jun 2023 dan melibatkan semakan data sekunder retrospektif kes *P. knowlesi* yang dilaporkan dalam sistem e-Vekpro di Pahang yang memenuhi kriteria inklusi yang telah ditetapkan. Analisis deskriptif dan pemetaan kadar insiden telah dijalankan. Analisis ketumpatan dan kluster dilakukan masing-masing menggunakan '*Kernel Density Estimation'* (KDE) dan *'Nearest Neighbour Index'* (NNI). Manakala '*Global Moran's I'* dan statistik LISA bagi autokorelasi di peringkat mukim. Analisis spatial dilakukan menggunakan perisian R versi 4.2.3.

Keputusan: Daripada 967 kes malaria *P. knowlesi* yang didaftarkan di Pahang dari 2011 hingga 2022, majoriti kes adalah lelaki (83.7%). Manakala purata umur ialah 36.9 (SD = 15.83), dan majoriti kes adalah Melayu (58.3%). Purata kadar insiden *P. knowlesi* selama 12 tahun di Pahang ialah 0.053 kes bagi setiap 1,000 penduduk dan menunjukkan tren menaik dan menurun, dengan kemuncaknya pada 2013, 2018, dan 2021. Daerah Lipis mempunyai kepadatan tinggi kes malaria *P. knowlesi*, bersama-sama dengan daerah bersebelahan iaitu Raub dan Jerantut. Kes *P. knowlesi* menunjukkan corak kluster (NNI <1) kecuali pada tahun 2011, 2015, 2016, dan 2019. Hasil analisis autokorelasi menunjukkan wujudnya positif korelasi ruangan pada tahun 2012 dan 2013, dan kawasan hotspot yang terletak di mukim Tembeling, Cheka, Kechau, Telang, dan Gua telah dikenalpasti.

Kesimpulan: Kadar insiden malaria *P. knowlesi* di Pahang telah menunjukkan tren turun dan naik dalam tempoh 12 tahun, dengan kemuncaknya dapat dilihat pada 2013, 2018, dan 2021, melalui kepadatan, pengelompokan dan korelasi yang lebih tinggi di mukim luar bandar di Pahang. Pihak berkuasa kesihatan awam harus mengutamakan pencegahan yang bersasar di kawasan berisiko tinggi yang dikenal pasti, termasuk meningkatkan pengawasan dan pemantauan populasi berisiko, mengukuhkan langkah kawalan vektor, dan melaksanakan inisiatif pendidikan masyarakat.

KATA KUNCI: *P. knowlesi*; malaria; insiden; kajian ruang-masa

INCIDENCE AND SPATIOTEMPORAL DISTRIBUTION OF PLASMODIUM KNOWLESI INFECTION IN PAHANG FROM 2011 TO 2022

ABSTRACT

Introduction: *Plasmodium knowlesi* malaria poses a significant public health challenge in Pahang and Malaysia, as it can result in severe and fatal malaria cases in humans. Moreover, this disease threatens efforts towards malaria elimination. An analysis of the incidence and spatiotemporal patterns of *P. knowlesi* malaria is necessary to gather crucial information for identifying high-risk areas, making informed decisions, and allocating resources effectively for malaria control and prevention.

Objective: The study aims to evaluate the incidence rate and spatiotemporal distribution of *P. knowlesi* infection in Pahang from 2011 to 2022.

Methodology: The study was a cross-sectional study conducted from January 2023 to June 2023, using a retrospective secondary data review of reported *P. knowlesi* cases that met the predefined inclusion criteria from the e-Vekpro system in Pahang. A descriptive analysis and mapping of the incidence rate were conducted. Density and cluster analysis were performed using Kernel Density Estimation (KDE) and Nearest Neighbour Index (NNI), respectively. While Global Moran's I and LISA statistics for autocorrelation at the subdistrict level. Spatial analysis was done using R software version 4.2.3.

Result: Of 967 confirmed *P. knowlesi* malaria registered in Pahang from 2011 to 2022, the majority were male (83.7%). The mean age was 36.9 (SD = 15.83), and the Malay predominants (58.3%). The average 12 years incidence rate of *P. knowlesi* in Pahang was 0.053 cases per 1,000 population and exhibited an upward and downward trend, with peaks in 2013, 2018, and 2021. The Lipis district has a high density of *P. knowlesi* malaria cases, together with the neighbouring districts of Raub and Jerantut. *P. knowlesi* cases exhibited clustering patterns (NNI <1) except for 2011, 2015, 2016, and 2019. The results of the autocorrelation analysis indicated the presence of positive spatial correlation during the years 2012 and 2013 and identified specific hotspot areas located in the subdistricts of Tembeling, Cheka, Kechau, Telang, and Gua.

Conclusion: The incidence rate of *P. knowlesi* malaria in Pahang has shown fluctuations over the course of 12 years, with peaks in incidence observed in 2013, 2018, and 2021, which were characterised by higher density, clustering, and correlation in rural subdistricts of Pahang. Public health authorities should prioritise targeted prevention in the identified high-risk areas, including enhancing surveillance and monitoring for populations at risk, strengthening vector control measures, and organising community education initiatives.

KEYWORDS: *P. knowlesi*; malaria; incidence; spatiotemporal study

CHAPTER 1

INTRODUCTION

1.1 Background

Malaria is an ancient disease that continues to have significant impacts on the health of the population nowadays. The history of malaria has been chronicled in many ancient documents dating back to the sixth century BC, despite the fact that Charles Louis Alphonse Laveran discovered malarial parasites only back in 1880 (Cox, 2010). It is a life-threatening disease caused by *Plasmodium* parasites and transmitted to humans through the bites of infected female *Anopheles* mosquitos (WHO, 2023). Four recognised species of *Plasmodium* infect humans nearly exclusively as their intermediate host; *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale*, and *Plasmodium malariae* (CDC, 2020). In 1932, a *Plasmodium* species with similar morphologic features to *Plasmodium malariae* was discovered. It was named *Plasmodium knowlesi*, in recognition of one of the two scientists that discovered it (Sabbatani and Fiorino, 2010).

In 1965, a man from the United States was diagnosed with *P. knowlesi* after travelling to Peninsular Malaysia. This is the first case recognised as a naturally infected *P. knowlesi* in humans (Chin *et al.*, 1965). *P. knowlesi* received huge attention after a large number of human infections were reported in the Sarawakian Kapit Division in 2004 (Singh *et al.*, 2004). Since then, *P. knowlesi* has been widely perceived as the parasite responsible for zoonotic malaria, and regarded as the fifth parasite that causes malaria in humans (White, 2008).

The World Malaria Report 2022 documented a significant increase in the incidence of *P. knowlesi* infections among people from certain countries across the

Southeast Asia Region, particularly in Malaysia. Nonetheless, the report lacks specific details regarding other regions with a high incidence of *P. knowlesi* malaria. At the same time, travellers returning from South East Asian nations have documented cases of *P. knowlesi* in China, Finland, France, Germany, Italy, Japan, New Zealand, Poland, Scotland, Spain, Sri Lanka, Sweden, and the United States (Lee *et al.*, 2022). While in Malaysia, since 2017, a total of 17,125 *P. knowlesi* cases and 48 deaths have been reported. In 2021 alone, 3,575 cases were reported, resulting in 13 deaths (WHO, 2022b). Furthermore, *P. knowlesi* cases increased exponentially in Malaysia, from 376 to 3,614 cases between 2008 and 2017, an 861% increment (Chin *et al.*, 2020), thus becoming a significant public health problem.

1.1.1 *Plasmodium knowlesi* infection severity

P. knowlesi is a significant disease that can potentially cause severe and fatal malaria in humans. Approximately 1 in 10 patients develop potentially fatal complications like multiorgan failure, hypoglycemia, and lactic acidosis, with a case fatality rate of 1.8% (Daneshvar *et al.*, 2009). In comparison with other types of malaria infection, patients with severe *P. knowlesi* infections are older. They also have a higher neutrophil count and creatinine level compared with patients with severe *P. falciparum* infections (Kotepui *et al.*, 2020). In addition, past studies reported parasitaemia is associated with disease severity in *P. knowlesi* malaria, which can be severe and fatal (Millar and Cox-Singh, 2015), with an average mortality rate in peninsular Malaysia of 0.012 per 100,000 (Hussin *et al.*, 2020).

Detecting the severity of *P. knowlesi* infection is of utmost importance, irrespective of the presence or absence of fever in the patient. It is noteworthy that recently a case has been reported in which a fatal infection of *P. knowlesi* malaria

occurred despite the absence of fever (Chang, 2023). Furthermore, Despite the availability of treatment for *P. knowlesi* malaria infection in the form of artemisinin combination therapy (ACT), it was still the most common cause of adult malarial death in Sabah between 2010 and 2014 (Rajahram *et al.*, 2016).

1.1.2 Challenges towards malaria elimination program in Malaysia

Malaria elimination, as proposed by the World Health Organisation (WHO), is to reduce the number of local cases in any geographical area to zero. Malaysia considers eliminating malaria as a viable option in order to maximise the benefits such as reduced health-care costs, greater productivity and level of population education, decreased school absenteeism, and the recruitment of foreign investment (MOH Vector Borne Disease Section, 2010).

According to Sustainable Development Goals Target 3.3, WHO put a target to end the epidemics of malaria, AIDS, tuberculosis, and other neglected tropical diseases (WHO, 2022a). Furthermore, Expert Consultation on Malaria Elimination Strategies Report listed that research prioritisation is needed on distribution, hotspots, maps of cases, vectors and macaques of *P. knowlesi* (WHO Western Pacific Region, 2017a).

Malaysia announced its intention to eliminate malaria, with a staged objective of attaining zero local transmission in West Malaysia by 2015 and in Sabah and Sarawak by 2020. The execution of the policy was outlined in National Strategic Plan For Elimination Of Malaria 2010–2020 (MOH and WHO, 2015). Since 2018, Malaysia has not recorded any indigenous cases of malaria that were caused by human malaria parasites. However, significant increments in zoonotic malaria can threaten Malaysia's plan to achieve malaria elimination status. The transition in malaria epidemiology from indigenous malaria to zoonotic malaria has had significant negative impacts on the

progress made by the Malaysian government in its effort to fight against the disease during the last half-century (Chin *et al.*, 2020).

1.2 Statement of problem

Malaysia is on the right path to achieving the elimination status of indigenous human malaria but facing the threat of exponentially rising cases of zoonotic malaria, *P. knowlesi*. According to statistical data, Pahang ranks fifth among Malaysian states with the highest incidence of *P. knowlesi* cases in 2022, following Sabah, Sarawak, Kelantan, and Perak (Pahang State Health Department, 2023)

P. knowlesi malaria can be severe and fatal and significantly impact the elimination and eradication of malaria. Furthermore, failure to control or eliminate malaria also carries significant economic implications towards agricultural development (Asenso-Okyere *et al.*, 2011), labour productivity and educational outcomes (Shretta *et al.*, 2016). Furthermore, based on the literature review, there is still no published study in terms of the spatiotemporal distribution of *P. knowlesi* in the Malaysian state of Pahang.

1.3 Rationale

P. knowlesi malaria incidence has a significant spatial and temporal heterogeneity even in a small area. Therefore, spatiotemporal analysis of *P. knowlesi* is essential in providing information to public health planners for resource allocation and decision-making. Geographic-based mapping also will identify hotspots of *P. knowlesi*. The information is vital for public health planners and stakeholders to formulate better

control and management strategies to improve the country's economy and patient outcomes.

The disease needs to be mapped on many different layers, from country level, district, sub-district and down to village level for efficient control measures, especially to relocate resources and field interventions. This study aims to address the current trend of rising *P. knowlesi* transmission, which will eventually contribute in achieving our country's Target 3.3 of the Sustainable Development Goals (SDGs).

1.4 Research questions

1) What is the trend of *P. knowlesi* cases in Pahang for 2011-2022?

2) What is the incidence rate of *P. knowlesi* cases in Pahang by subdistrict?

3) Is there spatial clustering of *P. knowlesi* cases in Pahang for 2011-2022?

4) Where are the hotspots of *P. knowlesi* cases in Pahang for 2011-2022?

1.5 Objectives

1.5.1. General objective

To study the incidence and spatiotemporal distribution of *Plasmodium knowlesi* infection in Pahang from 2011 to 2022.

1.5.2. Specific objectives

1) To describe the trend of *P. knowlesi* cases in Pahang for the year 2011-2022.

2) To describe the trend and map the incidence rate of *P. knowlesi* cases in Pahang by subdistrict.

3) To map the spatial clustering of *P. knowlesi* cases in Pahang for the year 2011- 2022.

4) To identify the hotspots of *P. knowlesi* cases in Pahang for the year 2011-2022.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

All the literature searches and reviews on spatiotemporal and *Plasmodium knowlesi* were done using search engines such as Google Scholar, Pubmed and Scopus platform. Various searching techniques were used, such as combining phrases with Boolean operators (AND, OR or NOT). Keywords used were malaria, *Plasmodium knowlesi*, spatial, temporal, incidence, prevalence, trend, rate, Geographical Information System, distribution and hotspot.

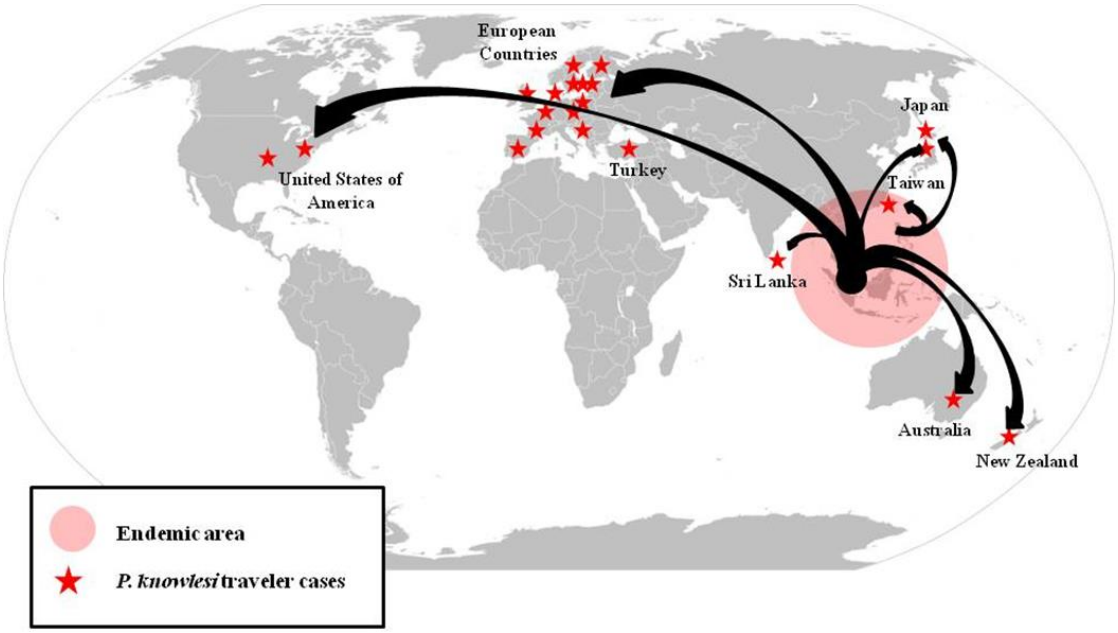
2.2 Epidemiology of *Plasmodium knowlesi* malaria

Plasmodium knowlesi is a zoonotic disease reported in all South East Asia countries except Timor Leste (Jeyaprakasam *et al.*, 2020) and is widely distributed in Malaysia (Cox-Singh *et al.*, 2008). It has a wide distribution throughout Southeast Asia, including in peninsular Malaysia and Borneo, as well as in Singapore, Thailand, Cambodia, Laos, Vietnam, Myanmar, and Indonesia (Karunajeewa and Berman, 2020). Out of 5,351 cases reported between 2004 and 2016 in South East Asia, 4,757 (88.9%) cases occurred in Malaysia, 465 (8.7%) in Indonesia, and 37 (0.7%) in Thailand (Zaw and Lin, 2019).

According to the World Malaria Report 2022, *P. knowlesi* infections among humans have significantly increased in some countries, particularly Malaysia. While in 2021, additional 435 *P. knowlesi* cases were reported in the WHO Southeast Asia Region, in Indonesia, the Philippines and Thailand (WHO, 2022b). *P. knowlesi* cases have been documented in a number of locations in Kalimantan and Sumatra, Indonesia.

South Kalimantan (Borneo Island), Aceh Besar, Batubara Langkat in Sumatra Island, and South Nias have all documented cases (Lempang *et al.*, 2022).

According to a systematic review, Indonesia recorded 545 indigenous cases of *P. knowlesi* malaria between 2010 and 2021. Of the account cases, a significant majority of 95.4%, or 520 cases, were documented within the time frame covering from 2017 to 2021 (Bin Said *et al.*, 2022). In addition, a Study in North Sumatera Indonesia showed 11.8% or 377 out of 3,731 participants harboured *P. knowlesi* parasite through active and passive detection (Lubis *et al.*, 2017). In the West of Indonesia, emerging evidence suggests that *P. knowlesi* may now be the predominant *Plasmodium* species in some districts (Barber *et al.*, 2017).



(Source: Jeyaprakasam *et al*., 2020)

Figure 2.1: *Plasmodium knowlesi* traveller cases with a history of visits to Southeast Asia

The return of travellers infected with *P. knowlesi* and subsequent transmission to their respective countries represents a significant global public health concern (Figure 2.1). According to reported studies, individuals returning from Southeast Asia were