

Article

Incidence of Malaria in Kuala Lumpur, Malaysia: A Single-Institution Retrospective Review from 2005 to 2020

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Abstract: While there has been a tremendous decline in malaria disease burden in the remote parts of the Malaysia, little is known about malaria incidence in its urban localities. This study aimed to analyse trends of malaria cases in urban Kuala Lumpur, Malaysia. All suspected cases presented to a university hospital in Kuala Lumpur from January 2005 to December 2020 were examined by microscopy. Infection status was analysed using descriptive statistics and curve estimation analysis. Of 3105 blood films examined, 92 (3%) were microscopically confirmed malaria cases. *Plasmodium vivax* infections accounted for the majority (36.9%) of all malaria cases. Nearly half (47.8%) of cases were found among foreign cases ($P < 0.001$). The majority of foreign cases were males (86.4%) and came from Southeast Asian countries (65.9%). Curve estimation analysis showed significant decreases of malaria cases due to *P. vivax* ($R^2 = 0.598$; $P < 0.001$) and *Plasmodium falciparum* ($R^2 = 0.0259$, $P = 0.029$), but increase for *Plasmodium knowlesi* ($R^2 = 0.325$, $P = 0.021$) during the 16 years. This study revealed that malaria incidence in urban Kuala Lumpur is low and has remained stable since 2005. However, *P. knowlesi* played a significant role in the increase of overall malaria in the area, highlighting the importance of continued vigilance and improved surveillance.

Keywords: malaria; *Plasmodium knowlesi*; trends; retrospective; incidence; Malaysia

1. Introduction

In the Western Pacific region categorised by the World Health Organization (WHO), there are 753 million people in 10 countries that are currently at risk of infections with malaria [1]. Malaysia, which is included in this region, is in the pre-elimination phase and continues to progress towards elimination, reporting only 85 cases of indigenous human malaria cases in 2017 [1]. Even though malaria control activities have significantly reduced human malaria incidence in Malaysia, the resurgence of the monkey malaria parasite *Plasmodium knowlesi* remains a main public health problem in the less developed areas of the country, especially in Malaysia Borneo [2-4] and among hard-to-reach populations of indigenous people (i.e. Orang Asli) in Peninsular Malaysia [5-8]. About one-third (32%) of total malaria cases occur in Peninsular Malaysia, and the majority of these are found in the central, south-eastern and northern coastal regions [9]. The remaining 68 percent of cases are found in Malaysian Borneo, primarily in the states of Sabah and Sarawak [10].

Malaysia reoriented its intent from malaria control to elimination in 2011, with a phased goal of achieving zero local transmission in Peninsular Malaysia by 2015, and in Sabah and Sarawak by 2020. Malaysia is vulnerable to malaria importation, primarily

from Indonesian and Filipino migrant workers seeking employment in Malaysia's growing economy [10,11]. In addition, many documented and undocumented migrants from Myanmar, Bangladesh, Nepal, Indonesia and Thailand also enter Peninsular Malaysia to serve the low-skilled and semi-skilled sectors of the economy, especially in the urban areas. In 2014, imported cases accounted for 20 percent of all cases in Malaysia [12]. In countries approaching elimination, imported cases tend to make up most of the recorded cases and threaten the re-establishment of malaria transmission in receptive areas [13]. As the country is dependent on foreign labour that comes from regional countries, the malaria elimination goal in Malaysia may be at risk.

Despite the significant decline in malaria disease burden in remote parts of Malaysia, the overall trend of malaria incidence based on passive case detection is not well-documented in urban localities. To our knowledge, there were few published data available on passive case detection of malaria in Malaysia since 2003. Epidemiological data such as trends of malaria positivity rates at public institutions and hospitals are essential to design appropriate interventions. Therefore, this study aims to describe the more recent epidemiological and trend of malaria cases diagnosed in the tertiary care referral and teaching hospital of Kuala Lumpur, Malaysia. As the hospital is located in the capital city, it serves as a proxy measure for the trend of malaria in the urban area which may contribute to evidence-based decisions on malaria control activities.

2. Materials and Methods

2.1 Study Area

This study was conducted at Hospital Canselor Tunku Muhriz (HCTM), a tertiary care referral and teaching hospital of the National University of Malaysia (UKM). The hospital is a major medical centre located in the capital city of Kuala Lumpur, Malaysia.

2.2 Study Design

This retrospective laboratory record review study was carried out to determine 16 years (January 2005 – December 2020) malaria cases. This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Research and Ethics Committee of UKM (Reference no: JEP-2018-055). The need for informed consent was waived by the committee considering the retrospective nature of the study.

2.3 Data Collection

The study participants were all malaria suspected individuals who had a complaint of febrile illness at HCTM during the study period. Sociodemographic and laboratory data regarding malaria were extracted from the electronic-based reporting system of HCTM and yearly laboratory log-books from the Department of Parasitology and Medical Entomology, Faculty of Medicine in UKM. Malaria diagnosis was based on microscopic examination of Giemsa-stained thick and thin blood smears. In HCTM, microscopic examination is the gold standard diagnostic method for detection and species identification of *Plasmodium* parasites. Peripheral smear examination of a well-prepared and well-stained thick and thin blood films were used to diagnose malaria in the laboratory. The hospital strictly follows Malaysia's standard operating procedures in all phases of the quality control for capillary blood sample collection, smear preparation, staining and blood film examination for malaria parasite detection. Blood films were fixed and stained with 3% Giemsa stain and examined under oil emersion (10x100 magnification) by trained microscopists. Blood films were defined as negative if no parasites were found after examining 100 high-power microscopy fields. For all positive samples, malaria species were identified and asexual parasite forms were counted against 500 leukocytes. Parasite density was estimated from parasite counts, assuming that there were 8,000 leukocytes per microliter (μL) of blood. For the remaining blood sample of positive cases, multiple blood smears were made and kept for educational purposes and future research.

2.4 Statistical Analysis

All the data was merged, cleaned and cross-checked using a Microsoft Excel spreadsheet. The data were analysed using STATA/SE version 13.1 (StataCorp, Texas, USA) and GraphPad Prism version 5.03 (GraphPad Software Inc., California, USA). A descriptive analysis was performed in order to assess yearly distribution, gender, age group, ethnicity and nationality. The Pearson’s Chi-square test, Fisher’s exact test and Kruskal-Wallis test were used to describe the association of variables. Curve estimation analysis was used to evaluate the trends of the data. A $P<0.05$ was considered statistically significant.

3. Results

Over a period of 16 years (2005 – 2020), 3105 blood films were requested for malaria diagnosis at HCTM, of which 92 (3%; 95% confidence interval [CI]: 2.4 – 3.6)) were microscopically confirmed malaria cases (Table 1). The median age of the malaria cases was 30 (interquartile range [IQR]: 25 – 39) years. The majority (71.7%, 95% CI: 61.4 – 80.6) of the infected were young adults (18 – 40 years) and the age distribution differed significantly between the infected and non-infected groups ($P = 0.007$). Individuals of Bumiputera ethnicity accounted for most of the malaria cases, but there was no significant difference in ethnic distributions between the infected and the non-infected groups. When compared to the non-infected group, malaria infections were significantly more common in males ($P<0.001$) and among Malaysian ($P<0.001$).

Table 1. Demographic characteristic of patients screened at University Hospital of the National University of Malaysia (UKM) in 2005-2020

Characteristics	Without malaria	With malaria	P-value ^a
No. of patients, N	3013	92	
Median age ^b (IQR), years	32 (24-48)	30 (25-39)	0.159
Age group, n (%)			
≤6	67 (2.5)	4 (4.4)	0.007
7 - 17	200 (7.4)	3 (3.3)	
18 - 40	1501 (55.8)	66 (71.7)	
>40	921 (34.3)	19 (20.6)	
Gender ^b , n (%)			
Male	1817 (61.9)	78 (84.8)	<0.001
Female	1116 (38.1)	14 (15.2)	
Malaysia's ethnic group, n (%)			
Bumiputera	1592 (68.9)	30 (62.5)	0.361
Chinese	524 (22.7)	15 (31.3)	
Indian	193 (8.4)	3 (6.2)	
Nationality ^b , n (%)			
Malaysian	2309 (81.2)	48 (52.2)	<0.001
Non-Malaysian	534 (18.8)	44 (47.8)	

IQR, interquartile range
^aChi-square test, Fisher's exact test or Kruskal-Wallis test comparing with and without malaria
^bNo data recorded for age (n = 324), gender (n = 80) and nationality (n = 170)

The trend of malaria cases is summarized in Table 2. Malaria cases were reported in all years except 2015, with the highest prevalence reported in 2018 (10.3%; 3/29). Overall,

	30	2	3	1	7	1	1	3	2	0	0	0	3	2	3	0	2
Bumiputera	(0.9)	(0.7)	(1.3)	(0.5)	(2.5)	(0.3)	(0.4)	(1.1)	(0.8)	(0.0)	(0.0)	(0.0)	(1.9)	(1.5)	(10.3)	(0.0)	(2.2)
	15	1	0	0	2	2	0	4	2	1	0	0	0	1	0	1	1
Chinese	(0.5)	(0.4)	(0.0)	(0.0)	(0.7)	(0.7)	(0.0)	(1.4)	(0.8)	(0.4)	(0.0)	(0.0)	(0.0)	(0.7)	(0.0)	(5.6)	(1.1)
	3	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0
Indian	(0.1)	(0.4)	(0.0)	(0.0)	(0.0)	(0.3)	(0.0)	(0.4)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
No. of cases by nationality, n (%)																	
	48	4	3	1	9	4	1	8	4	1	0	0	3	3	3	1	3
Malaysian ^c	(1.5)	(1.4)	(1.3)	(0.5)	(3.2)	(1.3)	(0.4)	(2.9)	(1.7)	(0.4)	(0.0)	(0.0)	(1.9)	(2.2)	(10.3)	(5.6)	(3.3)
	44	3	3	7	6	1	4	5	3	8	3	0	1	0	0	0	0
Non-Malaysian ^d	(1.4)	(1.1)	(1.3)	(3.2)	(2.1)	(0.3)	(1.5)	(1.8)	(1.2)	(3.5)	(1.8)	(0.0)	(0.6)	(0.0)	(0.0)	(0.0)	(0.0)
No. of cases among non-Malaysian, n (%)																	
	37	3	2	6	5	1	4	4	3	5	3	0	0	0	0	0	0
Asian ^e	(1.2)	(1.1)	(0.8)	(2.8)	(1.8)	(0.3)	(1.5)	(1.4)	(1.2)	(2.2)	(1.8)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
		0	0	1	1	0	0	1	0	3	0	0	1	0	0	0	0
African ^f	7 (0.3)	(0.0)	(0.0)	(0.5)	(0.4)	(0.0)	(0.0)	(0.4)	(0.0)	(0.9)	(0.0)	(0.0)	(0.6)	(0.0)	(0.0)	(0.0)	(0.0)

^aTotal cases of mixed-*Plasmodium* spp. infections: *P. falciparum*/*P. vivax* (n = 3), *P. falciparum*/*P. malariae* (n = 3); *P. vivax*/*P. malariae* (n = 1), *P. falciparum*/*P. knowlesi* (n = 1), *P. malariae*/*P. knowlesi* (n = 2) and *P. falciparum*/*P. malariae*/*P. knowlesi* (n = 1)

^bTotal male cases aged 18 and above: Malaysian (n = 38) and non-Malaysian (n = 34). Of the non-Malaysian males, 20 (59%) from Southeast Asia countries namely from Indonesia (n = 10), Myanmar (n = 9) and Vietnam (n = 1)

^cTotal malaria by species among Malaysian: *P. falciparum* (n = 11), *P. vivax* (n = 14), *P. malariae* (n = 2), *P. knowlesi* (n = 14) and mixed-species (n = 7)

^dTotal malaria by species among non-Malaysian: *P. falciparum* (n = 16), *P. vivax* (n = 20), *P. malariae* (n = 2), *P. knowlesi* (n = 2) and mixed-species (n = 4)

^eTotal cases by Asian countries: Myanmar (n = 16), Indonesia (n = 11), Pakistan (n = 3); Nepal (n = 2) and others (n = 5)

^fTotal cases by African countries: Nigeria (n = 3), Sudan (n = 3) and Ghana (n = 1)

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Plasmodium vivax, *Plasmodium falciparum*, *P. knowlesi*, *Plasmodium malariae* and mixed-*Plasmodium* spp. infections accounted for 36.9% (95% CI: 27.1 – 47.7), 29.3% (95% CI: 20.3 – 39.8), 17.4% (95% CI: 10.3 – 26.7), 4.3% (95% CI: 1.2 – 10.8) and 11.9% (95% CI: 6.1 – 20.4) of all malaria cases, respectively. No *Plasmodium ovale* infections were observed. The 11 cases of mixed-*Plasmodium* spp. infections were *P. falciparum*/*P. vivax* (n = 3), *P. falciparum*/*P. malariae* (n = 3), *P. vivax*/*P. malariae* (n = 1), *P. falciparum*/*P. knowlesi* (n = 1), *P. malariae*/*P. knowlesi* (n = 2) and *P. falciparum*/*P. malariae*/*P. knowlesi* (n = 1). *Plasmodium knowlesi* cases were first detected in 2010 and peaked in 2020, accounting for the majority of the cases that year.

Despite the apparent fluctuation over the 16-year period (Table 2), no significant difference was observed between years ($P = 0.082$). Similarly, the proportion of malaria cases from local and foreign patients was not significantly different between years ($P = 0.096$), with foreign cases contributed to essentially half (47.8%; 44/92) of all positive cases. Interestingly, out of 44 foreign cases, 38 (86.4%) were males and 29 (65.9%) came from South-east Asian countries. There were a total of 3 cases contributed solely by foreign patients in 2014 and a total of 10 cases solely by local patients between 2017 and 2020.

Albeit not significant, curve estimation analysis using linear models showed a slight increment of overall malaria positivity rates as well as in local cases from 2005 to 2020 (Figure 1a). In contrast, a significant reduction was observed in foreign cases from 2005 to 2020 ($R^2 = 0.313$, $P = 0.024$). With regards to *Plasmodium* species (Figure 1b), interestingly, significant reductions were observed for malaria due to *P. vivax* ($R^2 = 0.598$; $P < 0.001$) and *P. falciparum* ($R^2 = 0.0259$, $P = 0.029$), but not for *P. knowlesi* ($R^2 = 0.325$, $P = 0.021$) during the 16 years. As far as these models were used, *P. malariae* and mixed-infections did not show a significant increase across the years.

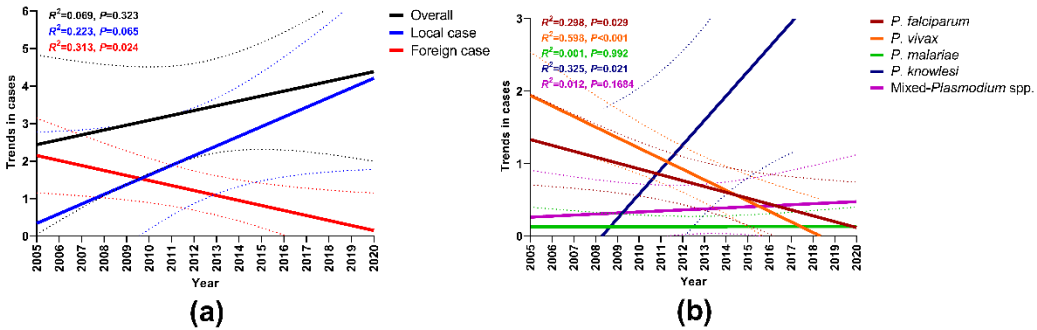


Figure 1. Curve estimation model for malaria cases by (a) nationality and (b) *Plasmodium* species. Solid lines show model predicted prevalence and broken lines are 95% confidence intervals (CI).

4. Discussion

Malaysia aims to achieve malaria elimination by the year 2020, and indeed the drop (98.4%) between 2010 and 2017 from a total of 4731 to 77 recorded indigenous cases for *P. vivax* and *P. falciparum* is highly promising [1]. However, the drop in the number of imported cases over the same period were less encouraging from a total of 831 to 423 recorded cases [1] and detected zoonotic *P. knowlesi* infections in remote parts of Malaysia have steadily increased [4,14-16]. In this study, we examined the available record data from a referral and teaching hospital of UKM located in the capital Kuala Lumpur, Peninsular Malaysia from 2005 to 2020. Over the 16 years, the number of malaria cases diagnosed annually at our hospital has remained relatively low and stable. The present study also revealed that the overall slide positivity rate of malaria was low (i.e. 3%), but high among males and non-Malaysian. This is similar to that of studies conducted in the same setting in 2003 [17,18]. Malaria species-specific data showed that *P. vivax* was the most

dominant species particularly in foreign cases with the estimated incidence showed a significant reduction over time. Moreover, the emergence of *P. knowlesi* infections in 2010 among local cases signify the alarming threat of zoonotic malaria in the country and may hinder malaria elimination efforts.

As one of the fastest-growing cities in Asia, where thousands of foreign workers arrived every year, Kuala Lumpur represents a likely hotspot for malaria importation in Malaysia. Our hospital in Kuala Lumpur received 44 (47.8%) confirmed malaria cases from foreigners over the period of 16 years (January 2005 to December 2020) of which 86.4% were males and 65.9% from neighbouring Southeast Asia countries. This finding was in line with the studies conducted in other Asian countries that highly rely on foreign workers such as Singapore [19,20], South Korea [21], Japan [22], Kuwait [23], Saudi Arabia [24], Qatar [25], and United Arab Emirates [26]. In 2017, imported cases in Malaysia accounted for 10.3% of all cases in the country [1]. There were more than 1.8 million registered migrants/foreign workers working in Malaysia in 2020. These migrants/foreign workers come from 12 different countries in Asia, and about 1.4 million of them were males (Department of Labour Peninsular, Ministry of Human Resources Malaysia, 2020). Rapid development in the city has led to an influx of low- and semi-skilled foreign workers and many of whom have come illegally or without work permits. In addition, there are significant numbers of displaced people in Kuala Lumpur with no nationality that arrive from malaria-endemic countries in Asia, particularly from Myanmar. Our finding also revealed that 16 out of 29 confirmed malaria cases from Southeast Asia were from Myanmar patients. As of January 2021, of the approximately 164,620 refugees and asylum-seekers registered with the United Nation High Commissioner for Refugees (UNHCR) in Malaysia, 86.5% were from Myanmar, 67% were males, and 16.8% of them had resettled in Kuala Lumpur [18]. As Malaysia moves toward elimination, malaria will begin to cluster among certain high-risk groups, including migrants and displaced populations. Improved surveillance, collaboration with key industries and other government agencies, and cross-border cooperation with neighbouring endemic countries are critical for addressing the ongoing threat of malaria importation and to achieve elimination.

In the present study, *P. vivax* was the most prevalent *Plasmodium* species detected, similar to what was found in the retrospective studies conducted in Peninsular Malaysia [7,17,27-30]. *Plasmodium vivax* has been the main cause of human malaria in Malaysia for the past 10 years and remains a health concern today [1,28]. In 2010, of the 5819 reported cases, 58.2% were due to *P. vivax* [1]. The ability of *P. vivax* to remain dormant in the liver as hypnozoites that can cause relapse following a primary infection, greater asymptomatic asexual carriage, and early gametocyte production provide far greater challenges for malaria elimination in the country. Nevertheless, no case of *P. vivax* was recorded in our hospital from 2015 to 2020 and based on the curve estimation analysis model, there was a significant reduction of *P. vivax* cases over the 16 years. This declining trend is a testament to the commitment of the government and other parties in Malaysia. The Malaysian Government launched the National Malaria Elimination Strategic Plan 2011-2020 with the ultimate goal of stopping locally-acquired malaria (except *P. knowlesi*) in Peninsular Malaysia by 2015 and in East Malaysia by 2020 [10]. The national strategic malaria elimination plan currently outlines seven key actions to achieve the elimination goal, including strengthening malaria surveillance system through an online system, intensifying control activities by indoor residual spray (IRS) and insecticide-treated nets (ITN), ensuring early case investigation, prompt treatment and management of outbreaks as well as enhancing community awareness and knowledge of malaria [31]. All these efforts have resulted in a significant reduction in overall malaria incidence in general and *P. vivax* cases in particular over the last decade.

Our work has provided insight into *P. knowlesi* cases in an urban area. Although the greatest number of *P. knowlesi* cases has been reported in remote areas in East Malaysia [2,9,12,32], the infection is also the predominant cause of malaria in Peninsular Malaysia [6,8]. It is unlikely that patients admitted to our hospital, acquired the *P. knowlesi* infection in the capital Kuala Lumpur (Federal Territory), which is considered a malaria-free area.

However, it is interesting to note that Kuala Lumpur is located within the State of Selangor, a malaria-endemic area in Peninsular Malaysia. In Selangor, local malaria transmission is still being reported from a few districts that adjoin sub-urban and forest range areas with rapid development and deforestation [30,33]. A similar link of deforestation and *P. knowlesi* malaria transmission has been observed recently in the State of Sabah, East Malaysia [34-36]. Except for a comprehensive case-control study by Grigg et al. on individual-level risk factors of acquiring *P. knowlesi* in villages in East Malaysia [37], no study has been conducted in Peninsular Malaysia. Furthermore, human behavioural factors may also be associated with acquiring knowlesi malaria. Activities appealing to urban populations such as jungle tracking, camping as well as waterfall picnic and fishing may increase exposure to environmental factors conducive to zoonotic transmission of knowlesi malaria. More detailed evidence about the risk of transmission in urban settings is required to design appropriate interventions.

5. Conclusions

Collectively, the malaria positivity rate in the study area is low and declining. The declining trend of the overall rate could be due to the significant decline of human malaria cases, particularly due to *P. vivax* and *P. falciparum* infections. However, malaria cases remain a public health concern in the urban setting with the influx of migrant workers and the increasing number of cases with *P. knowlesi* infections. Therefore, malaria case notification and interventions in Malaysia should be strengthened and reinforced to achieve elimination. Furthermore, improved surveillance of malaria clusters among certain high-risk groups displaced populations and migrant workers will require mutual collaboration with key industries and other government industries and cross-border cooperation with neighbouring endemic countries.

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Informed Consent Statement: The need for informed consent was waived by the Research and Ethics Committee of UKM considering the retrospective nature of the study

Data Availability Statement: Data is available upon request.

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