ORIGINAL ARTICLE

Factors Associated With *P. knowlesi* Clusters in Cleared Foci Areas in Sabah

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ABSTRACT

Introduction: *Plasmodium knowlesi* cases is increasing in trend despite integrated vector management leading to morbidity and death. This study determines the association between *P. knowlesi* cluster with vector control, risk factors and its spatiotemporal distribution in cleared foci area in Sabah. **Methods:** This is a cross sectional study between 2017 and 2019 involving *P. knowlesi* cases in cleared foci registered in Vekpro Online. Simple logistic regression tests were performed using Statistics Package for the Social Sciences (SPSS) software and spatiotemporal distribution mapped using Quantum Geographic Information System (QGIS) software. **Results:** A total of 4,739 cases were analysed and high *P. knowlesi* cases reported in Ranau (17.1%), Keningau (12.8), Tenom (10.8%), Kudat (8.1%) and Kota Marudu (7.2%). Younger age groups (0 – 9 years), the Rungus ethnicity, and the use of vector control measures were positively associated with *P. knowlesi* clusters with the odds ratio of 2.421 (95% CI [1.596, 3.674]), 2.654 (95% CI [1.899, 3.708]), and 2.559 (95% CI [2.175, 3.011]) respectively. However, age group of 50-59 years, male gender, occupations related to agriculture, and employment in the private sector or self-employed were negatively associated with *P. knowlesi* clusters in cleared foci in Sabah with odds ratio between 0.478 and 0.771. The prevalence of *P. knowlesi* in cleared foci in Sabah were 36.2%, 44.09% per and 41.59% per 100,000 population in 2017, 2018 and 2019 respectively. The distribution differs in districts. **Conclusion:** Tailored measures and spatiotemporal distribution of *P. knowlesi* cluster is useful to reduce transmission and aids focus-based planning.
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INTRODUCTION

Plasmodium parasites is the etiologic agent for malaria and can be transmitted to human through the bites of female Anopheles mosquito (1). A total of 229 million malaria cases and 409,000 deaths worldwide were reported in 2019 (1). Despite ready to be certified by World Health Organization (WHO) for zero indigenous human malaria, Malaysia particularly Sabah is still struggling with zoonotic malaria. The malaria elimination strategy in Malaysia directs the program to ensure termination of indigenous human malaria with assurance that every locality is stratified according to their vulnerability and receptivity towards disease transmission with application of vector control and surveillance activities accordingly (2,3). It is, therefore, plausible that with the present malaria program, the incidence of zoonotic malaria would also be reduced in a locality with applied vector control activities.

P. knowlesi, known as the fifth malarial parasite, did not pose health problems among humans until Singh et al. reported a naturally acquired Plasmodium from macaques to humans in Kapit division, Sarawak (4). Since then, *P. knowlesi* has been known to be more rampant in Southeast Asian countries like Malaysia, Brunei, Indonesia, and Myanmar (5). Between 2007 and 2018, Malaysia reported the highest cases of *P. knowlesi* (18,687 cases) and this were followed by Indonesia (418 cases), Brunei (73 cases), Myanmar (49 cases) and Thailand (44 cases) (5). The presence of zoonotic malaria displacing human malaria trends in Malaysia pose as a threat to the elimination program as it acts as proxy to the incidence of human malaria cases in affected areas (6-8). The Sabah state annual report of 2019 reported of a drastic reducing trend of total malaria cases in Sabah from more than 40,000 cases in 1996 to 2,047 in 2019. With the first *P. knowlesi* case detected in Sabah in 2007, the trend of zoonotic malaria increases from 703 cases in 2011 to 1,874 cases in 2019 (9, 10). This was seen despite the implementation of multiple surveillance, prevention, and control effort through the National Malaria Elimination Program (23). The mortality and morbidity between 2013 and 2017 by malaria are largely contributed to *P. knowlesi* (11).

Almost half of the global population is at risk of malaria. Most cases and deaths occur in the WHO African Region (26). Malaysia, however, is one of the 21 countries from five regions globally planned to achieve human indigenous malaria by 2020 (27). The last human indigenous malaria was reported in Malaysia was 2018 (27). Unfortunately, *P. knowlesi* is increasing in trend in Malaysia, particularly Sabah (8, 9). Despite being on track towards indigenous malaria elimination with implementation of integrated vector control and most localities in Sabah stratified as cleared foci, *P. knowlesi* incidence is still on the rise. WHO defined cleared foci as a defined area which is currently or previously malarious area with epidemiological and ecological factor which are vital for malaria transmission but has not reported human indigenous malaria for more than three years (28). Sabah and Sarawak contribute more than 75% reported cases of malaria annually in Malaysia. In the same study, approximately 77.1% *P. knowlesi* cases are reported from Sabah and Sarawak (10). This study is to further determine the association between *P. knowlesi* cluster with vector control, risk factors and its spatiotemporal distribution in cleared foci area in Sabah.

MATERIALS AND METHODS

The study design of this study is cross sectional located in the Sabah state of Malaysia. All *P. knowlesi* cases in cleared foci diagnosed by blood film malaria parasite (BFMP) and confirmed by polymerase chain reaction (PCR) registered in the Malaysian national malaria registry, Vekpro Online between 2017 to 2019 are included. The sample size was calculated using the formula using the difference in proportions formula and the sample size (n) calculated was 890. The prevalence of *P. knowlesi* cluster was taken as 82.9% (12). The difference in proportion (Malaysian and non-Malaysian) was set at 12.3% with 80% power and 1.96 statistical significance.

$$n = (Z_{\alpha/2}+Z_{\beta})^2 \times [p_1(1-p_1) + p_2(1-p_2)] / (p_1-p_2)^2$$

The Malaysian Infectious Disease Prevention and Control Act 1988 stated mandatory notification of every malaria case and must be registered into the national database, e–notifikasi and Vekpro Online system whereas all malarious area are stratified according to the risk of malaria transmission and will be updated to MyFOCI system. This study uses data obtained from both Vekpro Online and MyFOCI system that entails reported local *P. knowlesi* cases in Sabah and data on stratification of malarious foci in Sabah between 2017 to 2019 respectively. Eligible criteria include all *P. knowlesi* cases diagnosed by positive BFMP and confirmed by PCR in cleared foci. All human malaria cases imported *P. knowlesi* cases and *P. knowlesi* reported in active and residual non-active foci reporting local transmission of human malaria were excluded from this study.

Data obtained from Vekpro Online and myFoci system was extracted and data cleaning done using Microsoft Excel and subsequently analysed using IBM Statistical Package for the Social Science (SPSS) version 27 software with significance of $p<0.05$ and confidence interval of 95%. The association between the variables is statistically analysed and tested using simple logistic regression test. The annual *P. knowlesi* cases in Sabah for each focus was mapped and spatial distribution including point analysis, pattern analysis and cluster analysis done using QGIS software which is a free geographical information system software.

This study was registered under the National Research Medical Registry (NMRR-210242-58545) with approval code from UMS (JKEtika 1/21 (5)).

RESULTS

A total of 6,367 malaria cases were reported in Sabah as recorded in Vekpro Online between 2017 to 2019 in which 241 were human malaria cases, 8 imported *P. knowlesi* cases, and 1,379 were in active and residual non – active focis. Therefore, 4,739 cases of indigenous *P. knowlesi* cases in cleared foci ranging from the age of 2 months to 95 years old with the mean age of 36.8 years were analysed. The highest total cases were reported by Ranau district (17.1%) followed by Keningau (12.8%), Tenom (10.8%), Kudat (8.1%) and Kota Marudu (7.2%) districts as shown in Table I. The cases were classified into cluster and non-cluster to indicate the significance of zoonotic malaria transmission within the area. *P. knowlesi* cluster is the report of two or more *P. knowlesi* cases in the same locality within 14 days of date of onset whereas non-cluster was one case within 14 days in the same locality. Therefore, differentiating these two factors indicated the transmissibility of zoonotic malaria

Table I: Distribution of *P. knowlesi* Cluster in Cleared Foci Between 2017 to 2019 According to District in Sabah

District	n (%)	*P. knowlesi*	
		Non-cluster n (%)	Cluster n (%)
Ranau	810(17.1)	609(15.5)	201(24.8)
Keningau	606(12.8)	535(13.6)	71(8.8)
Tenom	513(10.8)	456(11.6)	57(7.0)
Kudat	386 (8.1)	254(6.5)	132(16.3)
Kota Marudu	339(7.2)	253(6.4)	86(10.6)
Tongod	335(7.1)	272(6.9)	63(7.8)
Lahad Datu	217(4.6)	193(4.9)	24(3.0)
Nabawan	213(4.5)	182(4.6)	31(3.8)
Beluran	203(4.3)	179(4.6)	24(3.0)
Sipitang	194(4.1)	191(4.9)	3(0.4)
Tawau	184(3.9)	155(3.9)	29(3.6)
Tambunan	181(3.8)	151(3.8)	30(3.7)
Kinabatangan	128(2.7)	120(3.1)	8(1.0)
Pitas	113(2.4)	94(2.4)	19(2.3)
Kota Belud	78(1.6)	71(1.8)	7(0.9)
Tuaran	73(1.5)	67(1.7)	6(0.7)
Kunak	45(0.9)	34(0.9)	11(1.4)
Beaufort	31(0.7)	29(0.7)	2(0.2)
Papar	31(0.7)	28(0.7)	3(0.4)
Semporna	28(0.6)	24(0.6)	4(0.5)
Sandakan	16(0.3)	16(0.4)	0(0.0)
Penampang	15(0.3)	15(0.4)	0 (0.0)
Total	4739 (100.0)	3928 (100.0)	811 (100.0)

in the locality (I.e., more cases may indicate higher transmissibility). The *P. knowlesi* cases reported were predominantly non-cluster in all parameters as shown in Table II. *P. knowlesi* cases were more noticeable among individuals between 20- and 49-year-old, and male gender for both cluster (78.8%) and non-cluster cases (82.8%). The cases reported were more among Malaysians (90.4% of non-cluster cases and 90.3% of cluster cases), mainly among Kadazan-Dusun-Murut ethnicities (71.8% of non-cluster cases and 64.2% of cluster cases). Individuals working in agriculture sector were more prominent among the *P. knowlesi* cases (58.8% among non-cluster cases whereas 54.6% among cluster cases) and least among those working in the armed forces sector (0.7% among non-cluster cases and 1.2% among cluster cases). Furthermore, among the *P. knowlesi* cases, 43.3% of non-cluster cases and 44.4% of cluster cases were transmitted peridomestically and predominantly occurring in areas without vector control like IRS and ITN (80.8% of non-cluster cases and 62.3% of cluster cases).

Table II also presents significant association ($p < 0.05$) between sociodemographic factors with *P. knowlesi* clusters in clear foci area in Sabah which includes age, gender, ethnicity, and occupation. The analysis shows that younger age group between the age of 0 – 9 years old are twice more likely to be in a clustered *P. knowlesi* infection (p = 0.000, OR = 2.421, 95% CI (1.596, 3.674)). The Rungus ethnicity is 2.6 times more

Table II: Association between sociodemographic factors and vector control with *P. knowlesi* clusters in cleared foci area in Sabah

Variables	*P. knowlesi*		Crude OR (95% CI)	X^2	*p value*
	Non-cluster n (%)	Cluster n(%)			
Age group (years)					
0-9	91 (1.9)	50 (1.1)	2.421 (1.596 – 3.674)	17.281	0.000*
10-19	474 (10.0)	134 (2.8)	1.246 (0.921 – 1.686)	2.027	0.155
20-29	800 (16.9)	153 (3.2)	0.843 (0.630 – 1.128)	1.326	0.250
30-39	937 (19.8)	177 (3.7)	0.832 (0.627 - 1.106)	1.602	0.206
40-49	702 (14.8)	124 (2.6)	0.778 (0.575 - 1.053)	2.641	0.104
50-59	545 (11.5)	87 (1.8)	0.703 (0.508 - 0.974)	4.482	0.034
60 and above	379 (8.0)	86 (1.8)	1.00		ref
Gender					
Female	675 (17.2)	172 (21.2)	1.00		ref
Male	3253 (82.8)	639 (78.8)	0.771 (0.639 - 0.930)	7.386	0.007
Ethnicity					
Kadazan-Dusun-Murut	2814 (71.8)	521 (64.2)	0.921 (0.705 – 1.202)	0.369	0.544
Bajau/Bugis	194 (4.9)	46 (5.7)	1.179 (0.785 – 1.771)	0.630	0.427
Rungus	223 (5.7)	119 (14.7)	2.654 (1.899 – 3.708)	32.712	0.000*
Melayu/Brunei	59 (1.5)	11 (1.4)	0.927 (0.465 – 1.849)	0.046	0.830
Others	263 (6.7)	40 (4.9)	0.756 (0.499 – 1.146)	1.732	0.188
Non-local ethnicity	368 (9.4)	74 (9.1)	1.00		ref
Nationality					
Malaysian	3549 (90.4)	732 (90.3)	0.990 (0.767 - 1.277)	0.007	0.935
Non-Malaysian	379 (9.6)	79 (9.7)	1.0		ref
Occupation					
Logging and Forestry	260 (6.6)	57 (7.0)	0.819 (0.550 – 1.219)	0.971	0.324
Agriculture	2311 (58.8)	443 (54.6)	0.716 (0.534 – 0.961)	4.967	0.026*
Armed Forces	29 (0.7)	10 (1.2)	1.288 (0.596 – 2.781)	0.414	0.520
Government Sector	83 (2.1)	16 (2.0)	0.720 (0.394 – 1.314)	1.145	0.285
Private Sector	558 (14.2)	98 (12.1)	0.656 (0.462 – 0.930)	5.594	0.018*
Self-employed	125 (3.2)	16 (2.0)	0.478 (0.265 – 0.861)	6.033	0.014*
Student	323 (8.2)	107 (13.2)	1.237 (0.870 – 1.759)	1.404	0.236
Unemployed	239 (6.1)	64 (7.9)	1.00		Ref
Peridomestic transmission					
No	2227 (56.7)	451 (55.6)	1.00		Ref
Yes	1701 (43.3)	360 (44.4)	1.045 (0.897 - 1.217)	0.322	0.570
Vector control (ie. IRS, ITN)					
No	3176 (80.8)	505 (62.3)	1.00		Ref
Yes	752 (19.2)	306 (37.7)	2.559 (2.175 – 3.011)	128.101	0.000*

likely to develop *P. knowlesi* cluster in cleared foci area (p = 0.000, OR = 2.654, 95% CI (1.899, 3.708)) compared to non–local ethnicities. The study also support some measure of protective factors among individuals working in the agriculture sector (p = 0.026, OR = 0.716, 95% CI (0.534, 0.961)), private sector (p = 0.018, OR = 0.656, 95% CI (0.462, 0.930)), and self – employed individuals (p = 0.014, OR = 0.478, 95% CI (0.265, 0.861)) which were 29%, 35% and 53% respectively from clustered *P. knowlesi* infection compared to unemployed individuals. In this study, cluster *P. knowlesi* infection were 2.6 times more likely to occur among individuals living in localities with vector control (p = 0.000, OR = 2.559, 95% CI (2.175, 3.011)). There were no significant association between nationality or peridomestic transmission of *P. knowlesi* with *P. knowlesi* cluster.

The observed years between 2017 and 2019 seasonal peaks of *P. knowlesi* cases between May and August and December and January as shown in Fig. 1. Fig. 2 shows the spatiotemporal distribution of *P. knowlesi* clusters in cleared foci area in Sabah from 2017 to 2019 which were concentrated along the Crocker Range towards Kudat district. *P. knowlesi* clusters were distributed in districts that were similarly reporting more sporadic *P. knowlesi* cases. The clustered *P. knowlesi* cases were observed in the district with more cases in 2017 but the trend evolved in 2018 and 2019. In 2018, the clustering of cases was observed to be concentrated in the Northern districts of Sabah like Kudat and Kota Marudu, despite the obvious increase of sporadic *P. knowlesi* cases in other districts and a more dispersed events of *P. knowlesi* clusters reported in 2019.

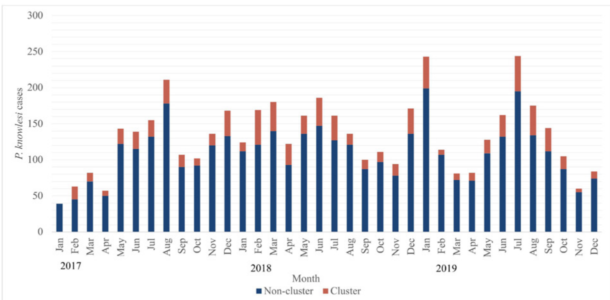

Figure 1: *P. knowlesi* Cluster and Non – cluster Cases Trend in Cleared Foci Area, 2017 – 2019. Clustered and non – clustered *P. knowlesi* (n = 4739) distribution in cleared foci area in Sabah.

DISCUSSION

P. knowlesi clusters in this study shows a significant association with young children between 0 to 9 years old who were more predisposed to cluster occurrence, whereas the age group between 50 to 59 years old seems to have a protective property against cluster. A finding in Kudat by Barber et. al. describes a wide age

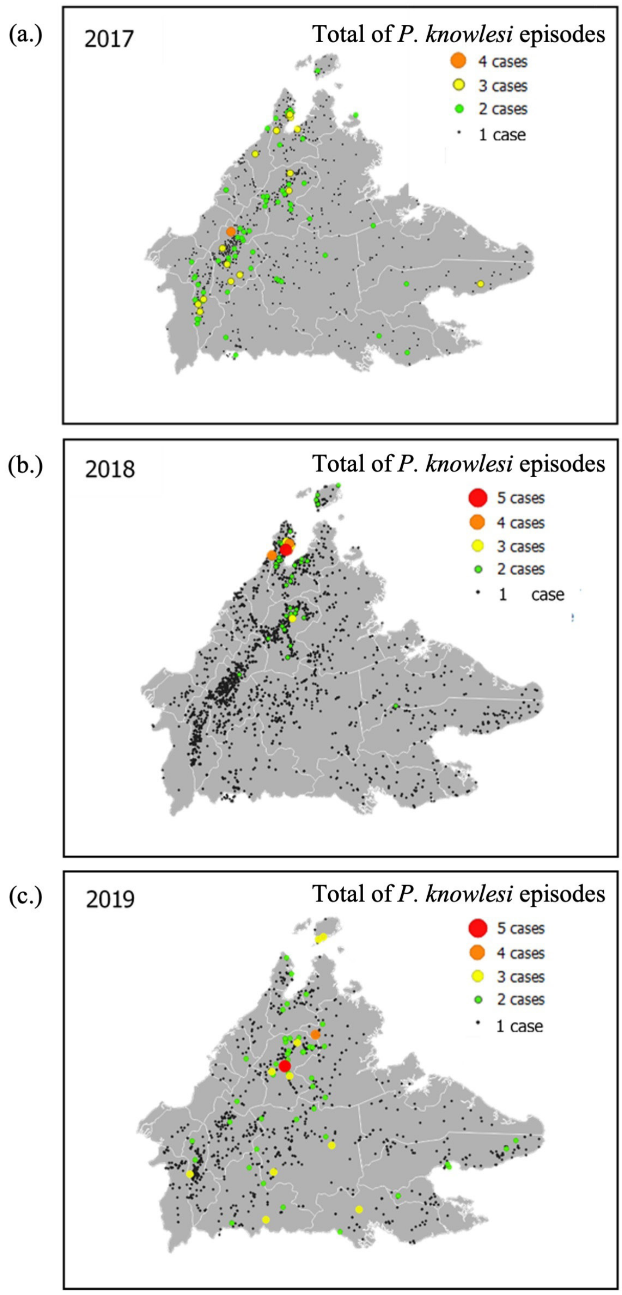

Figure 2: Spatiotemporal Distribution of *P. knowlesi* Cluster in Cleared Foci Area in Sabah from 2017 to 2019 (a.) 2017 (b.) 2018 (c.) 2019. Spatiotemporal distribution of *P. knowlesi* cases over three years using QGIS software.

distribution of *P. knowlesi* which predominantly affect villagers peridomestically. This was evidenced by the reports of *P. knowlesi* clusters among family members involving young children (13). Similar finding of wide age distribution was seen in a study in Sandakan (14). Children are more likely to be predisposed to clustered *P. knowlesi* cases as they are more likely to be close to their caretaker who are also exposed to the similar risk of transmission at the same time. Adults on the other hand could work or perform high risk activities on individually without the presence of other individuals, therefore avoiding transmission of *P. knowlesi* among multiple individual (I.e., cluster case).

Although *P. knowlesi* predominantly affect male gender, in this study male gender shows protective effect against *P. knowlesi* clusters. Previous studies supported the significant association of male gender with *P. knowlesi* cases (15). The fact that most *P. knowlesi* cases in previous studies including this study are predominantly male may be significant, explaining the significant findings among male gender has higher predisposition to perform high risk activities or behaviour related to *P. knowlesi* exposure. The ethnicity in Sabah is considered minorities when considering the whole Malaysian countries in which 60% of the population in the state are indigenous. The largest minorities include 17.8% Kadazan-Dusun, 14.0% Bajau, and 3.2% Murut (30). Despite Kadazan, Dusun and Murut (KDM) group of ethnics at most predisposed to acquiring *P. knowlesi* infection, the Rungus ethnic seems to be at more risk to acquire a clustered infection. This study shows a significant increase of the Rungus ethnicity towards *P. knowlesi* clusters, however there are no significant findings relating different ethnicity in Sabah to *P. knowlesi* cases (12). The Rungus ethnicity is more predominantly found in Kudat district (29) which also reported second highest cluster cases (16.3%) compared to other districts in Sabah. The KDM ethnicity are traditionally farmers, and in this study found them to be involved in agriculture activities like farming and planting paddy. Furthermore, findings in this study showed this ethnicity group to be involved in activities in the forest, farm and peridomestically which is explained by the lifestyle and living environment conducive for malaria transmission.

The significant association of occupational background to *P. knowlesi* clusters in this study was reflected in individuals who are involved in the agricultural sector, self – employed and private sector. Private sectors include individuals working in the construction sectors, photographers, security officer, business owners and contract workers (i.e., Cleaner, electrician). In recent years, development led to deforestation and land exploitation leading to migration of vectors and reservoir (16). Agricultural activities like farming, working in plantation, land clearing and those involving staying overnight in malarious area like the forest are seen to increase the risk of acquiring *P. knowlesi* infection (15,17). Some districts like Matunggong and Limbuak however revealed that the farming and plantation activities are near the homes, contributing to increased peridomestic transmission (18). This predisposes workers working in the private sectors, and unemployed individuals who are at the vicinity of the homes to be exposed to *P. knowlesi* infection (19). Findings of presence of macaques and malaria vectors at forest fringe and peridomestically strengthens this possibility. Although agriculture and private sectors, and self – employed individuals are shown to have a protective effect against *P. knowlesi* cluster, there are insufficient studies to support this.

We found that peridomestic infection is not significantly associated with the occurrence of *P. knowlesi* cluster. This may be resulting from the use of vector control like insecticide treated bed nets (ITN) and indoor residual spray (IRS) on the premises like their homes and barns, reducing the risk of malaria transmission among the local population, compared localities without vector control are highly reliant on the individuals' personal protective behaviour like the use of repellent and long-sleeved shirts and long pants which was not explored in this study. Recent studies have reported peridomestic transmission evidenced by cases reported among younger children. A pilot study using a new Deltamethrin formulation for the execution of IRS and outdoor residual spray (ORS) in Tenom proved effective control of *P. knowlesi* transmission with the observed reduction of reported cases in the study area followed by a drastic increase of cases once the IRS and ORS stopped (20). This may be effective for peridomestic areas with application of IRS and ORS as long-lasting insecticidal nets (LLIN) or ITN is not effective for *P. knowlesi* transmission (15,16). As many *P. knowlesi* cases are still reported non – peridomestically, other methods of prevention like sufficient personal protective equipment (PPE), repellent and prophylaxis are essential (16).

The study of association between vector control program implementation (I.e., ITN and IRS) and level of parasitaemia among the community in several sub – Saharan countries reveals a strong connection with rainfall and surface temperature which affect which show increased variation of parasitaemia (21). Implementation of vector control may reduce the vector density surrounding buildings and living spaces as was also seen in Vietnam, which displaces the malaria vectors to forest or forest fringe and found to be active from dusk to dawn (22). Hence why, more community members were at risk to acquire malaria infection when communing through these paths in Vietnam as mentioned by the author. Similar situations are experienced by our local communities especially in areas with agriculture or forest fringe located near their homes (18). The vector control in this study were IRS or/ and ITN as outlined by the Ministry of Health (MOH) Malaysia which are the core vector control method for malaria but was not specified for each locality in the Vekpro Online system (3). Therefore, despite vector control posing a significant association with *P. knowlesi* cluster, identifying the exact vector control modality in relation to *P. knowlesi* cluster and cases in this study were lacking.

The seasonal trend of *P. knowlesi* cases and clusters are also seen in other studies which suggest association of climate and rainfall especially between the month of April and July (24). Sabah has a rich ecological diversity which include 3.9 million hectares of forest reserves, parks, and wildlife sanctuaries with a monsoon system leading to cyclical pattern of wind flow (31).

This ecology and climate are favourable for malaria transmission. The spatial distribution of *P. knowlesi* cases in Sabah is seen predominantly affecting the area along the mountainous area of Crocker Range in Sabah state. A geo – epidemiology study of malaria distribution in Mali supported the close association between reported malaria cases with proximity of river, agriculture areas, topped with low median of rainfall and lowlands which significantly increase the risk of malaria transmission (25). On the Borneo Island, the *P. knowlesi* reservoir is found to reside in logged compared to unlogged forest, secondary forest, forest perimeters and most times close to human activities and peridomestic areas (26). This explains the distribution of sporadic *P. knowlesi* and clustered cases that are more concentrated but still occurring throughout different districts in Sabah between 2017 and 2019.

This study focuses the analysis of *P. knowlesi* in cleared foci area which has not reported human malaria for at least three years which was deficient in recent studies. It expresses the sociodemographic factors related to *P. knowlesi* among communities in malarious areas free from human malaria transmission. The use of spatiotemporal information aids in identifying malarious area requiring more attention and resources during planning and program development. However, the cases accounted in this study refers to individual cases and results may reflect the individual characteristic of case related to *P. knowlesi* clusters and not the cluster per se.

CONCLUSION

In conclusion, although Malaysia has achieved malaria elimination status, the increasing numbers of *P. knowlesi* reported should not be taken lightly as *P. knowlesi* is the proxy to human malaria transmission. The stratification of malarious area to cleared foci does not promise the absence of threat from zoonotic malaria. With continuous evaluation of trend of *P. knowlesi* sporadic and clustered cases, future management in specific areas can be commended for a focus-based planning, whether involving peridomestic vector control or other methods to reduce zoonotic malaria transmission. *P. knowlesi* has now proven to be more worrying in the future of malaria control especially in Malaysia if it proves to cause more morbidity and mortality burden among our community. Essentially, increasing zoonotic malaria incidence in Malaysia hampers the certification of malaria elimination by WHO and prevent an overall health achievement of both Malaysia and globally.

The use of vector control like IRS, ITN or LLIN and ORS in the elimination malaria program in sync with zoonotic malaria control may not be sufficient to ensure a diminished *P. knowlesi* transmission in the community. This is largely because despite peridomestic transmission of *P. knowlesi*, predominant cases are still occurring in non – peridomestic areas like the forest and agricultural areas such as plantation, farm, and paddy field. Prevention of zoonotic malaria would still be a priority by stopping transmission rather than treating and already infected patient despite being a challenging feat. Health education and behavioural change towards malaria transmission through chemoprophylactic method, use of repellent and proper clothing during high-risk activities are therefore important in prevention of the transmission.

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