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Host and Environmental Factors that Influence Plasmodium Knowlesi Malaria Infection in Humans: A Systematic Review

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Abstract

Introduction: *Plasmodium knowlesi* (*P.knowlesi*) is a zoonotic malaria parasite, transmitted between non-human primate hosts by the Anopheles (An.) mosquitos, and causing spill-over infections in humans where the parasite, vector, host, and human converge.

Methods: The search was done electronically to explore for appropriate papers *via* PubMed, and Science Direct for articles published up to March 2020, containing the words "factors associated" or "environmental factors" or "individual factors" or "ecological factors" and "*P.knowlesi*" and "human" including synonyms and Medical Subject Heading (MeSH) terms. A total of 27 articles from PubMed Databases and 18 articles from Science Direct were selected to be assessed for eligibility. Out of it, a total of 13 articles were selected to be analysed.

Results: Host factors such as sex and age, as well as occupation as individual factors, while environmental factors such as rainfall and geographic elevation have some association with *P.knowlesi* infection in humans. This zoonotic malaria poses unique challenges that will need to be addressed if all forms of malaria are to be eliminated based on the sustainable development goal (SDG).

Conclusion: This article highlights the importance of disease ecologies such as climate and landscape and human-environment interactions such as the land use patterns, such as agriculture or infrastructure activities) to reduce the further increase of cases and mortality globally due to *P.knowlesi* infection. This review focuses mainly on the host and environmental factors that influence *P.knowlesi* Malaria Infection in Humans.

Keywords: *Plasmodium knowlesi*, Zoonotic malaria, Malaria elimination, Human-environment interaction, Systematic review

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Introduction

World Health Organization (WHO) Malaria Report 2019 reports that 228 million cases of malaria occurred worldwide in 2018 compared with 251 million cases in 2010 and 231 million cases in 2017. The WHO African Region still bears the largest burden of malaria morbidity, with 213 million cases (93%) in 2018, followed by the WHO South-East Asia Region (3.4%) and the WHO Eastern Mediterranean Region (WHO, Malaria, 2020). Plasmodium knowlesi (*P.knowlesi*) is a zoonotic malaria parasite, transmitted between non-human primate hosts by the Anopheles (An.) mosquitos, and causing spill-over infections in humans where the parasite, vector, host and human converge (Abeyasinghe R. 2016). *P.knowlesi* was first isolated from a macaque imported into India from Singapore. *P.knowlesi* is now recognized as the fifth species of Plasmodium causing malaria in humans (Preis, J. *et. al.*, 2014).

P.knowlesi has a case fatality rate of around 1.7 per 1000 cases (6 deaths in total) (Rajahram, G.S. *et. al.*, 2019). *P.Knowlesi* has been reported to have at least 3-fold greater risk of severity than *P.falciparum* (Barber, B.E. *et. al.*, 2013). *P.knowlesi* acquisition risk factors related to behaviour or environment currently remain poorly defined (Grigg, M.J., *et. al.*, 2014). Therefore, it is important to understand the factors that contribute to the spillover of this zoonotic malaria to human to take the necessary measures to reduce the transmission among humans. Development of appropriate, practical and effective public health measures to control or prevent vector-borne diseases usually requires the assessment of all components and their interactions, and much remains to be elucidated, in particular the complex biological and ecological relationships that exist among pathogens, vectors, hosts and their environments (Carneiro, T.C., *et. al.*, 2017).

The vector that carried *P.knowlesi* is the *Anopheles spp*., such as the *An. leucosphyrus*, *An.latens*, An.*balabaensis* and *An.cracens* (Abeyasinghe R. 2016). The intermediate reservoir for *P.knowlesi* is the Long-tailed macaque (*M.fascicularis*), Pig-tailed macaque (*M.nemestrina*) and Banded leaf monkey (*P.melalophus*). Humans can be infected by *P.knowlesi* if they are fed upon by an infected mosquito (Preis, J. *et. al.*, 2014). A variety of factors intrinsic to the host, sometimes called risk factors, can influence an individual's exposure, susceptibility, or response to be infected by *P.knowlesi*. Susceptibility and response to the infection are influenced by individual factors such as genetic composition, nutritional and immunologic status, presence of medications, and psychological factors (CDC: USDHHS, Section 2, 2012). Environment refers to extrinsic factors that affect the agent and the opportunity for exposure. Environmental factors include physical factors such as geology and climate, biologic factors such as insects that transmit the agent, and socioeconomic factors like crowding, sanitation, and availability of health services (CDC: USDHHS, Section 8, 2012).

By systematically integrating these evidentiary sources, this article highlights the importance of disease ecology (e.g., climate & landscape) and human-environment interactions (e.g., land use patterns, such as agriculture or infrastructure activities) to reduce the further increase of cases and mortality globally due to *P.knowlesi* infection in accordance to the Sustainable Developmental Goal (SDG).

Goal 3 Target 3.3 of the SDG aims to "end the epidemics of AIDS, tuberculosis, malaria & neglected tropical diseases" by the year 2030 (WHO, 2019). This review focuses mainly on the host and environmental factors that influence *P.knowlesi* Malaria Infection in Humans. It is important to know these factors so that necessary prevention measures can be taken as well as in the education of the community on the risk factors of *P.Knowlesi* infection.

Methods

Various study designs were included but most of the study was expected to be observational designs. Papers that are published in all languages and dates from all over the globe were reviewed. Exclusion includes all non-primary literature, such as dissertations, theses, protocol studies and clinical guidelines. The search was done electronically to explore for appropriate papers *via* PubMed, and Science Direct for articles published any period of time up to March 2020, containing the words "factors associated" or "environmental factors" or "individual factors" or "ecological factors" and "*P.knowlesi*" and "human" including synonyms and Medical Subject Heading (MeSH) terms.

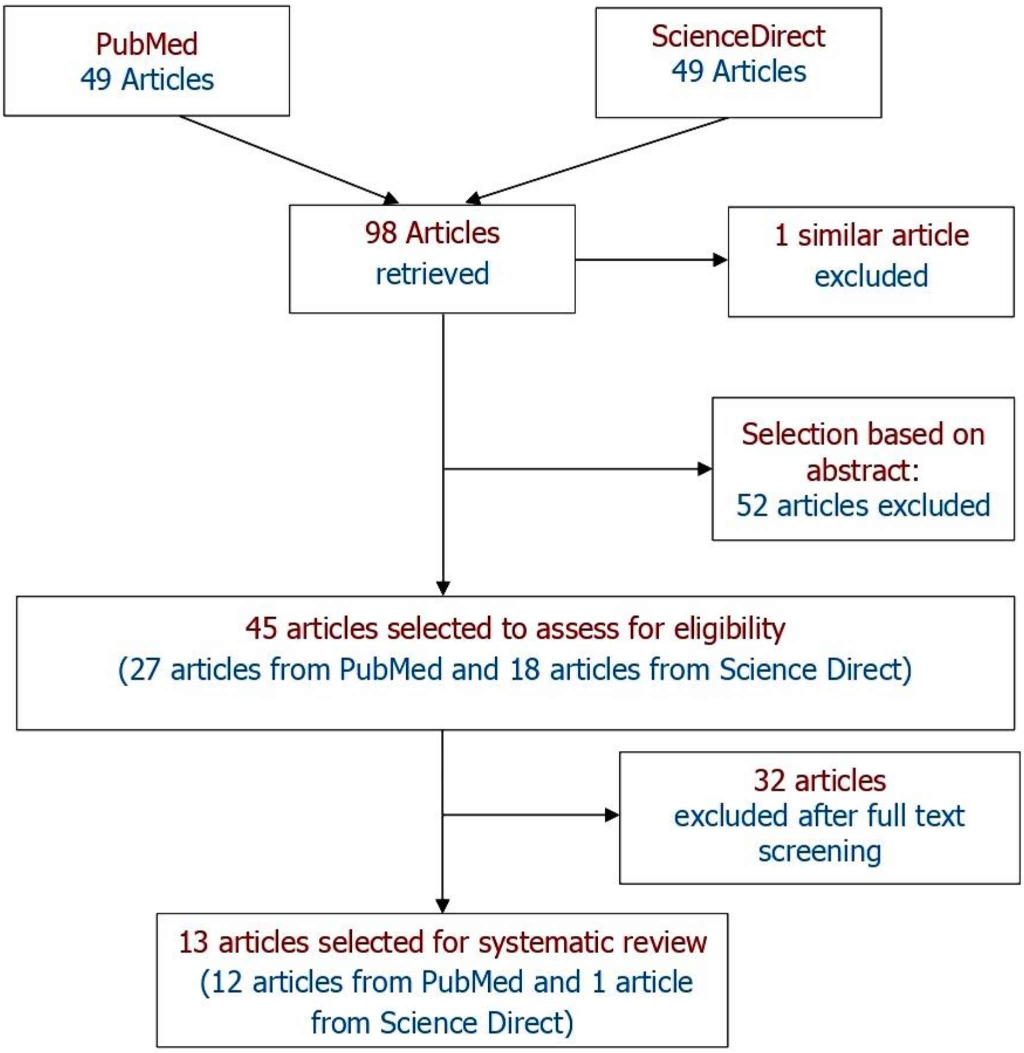

Figure 1: Summary of the article selection

Relevant references cited within these articles were also reviewed. Records that matched the inclusion criteria were selected and those that matched the exclusion criteria were excluded. The selected studies were screened by titles and abstracts by two reviewers. All data reviewed were presented in text and summary tables. Both databases gave 49 results upon the word search. Book chapters were excluded from the search. After removing the similar articles, 97 articles were screened through by reading the abstract. A total of 27 articles from PubMed Databases and 18 articles from Science Direct were selected to be analyzed but only 13 articles were finally selected for this review (**Figure 1 & Table 1**).

Results

Host factors

There are many individual factors that were found to be associated with *P.knowlesi* infection in humans. It can be divided into biological factors such as age and sex, medical history, genetic factors such as genetic diseases, occupation and behavioral factors. One of the articles found that age 15 years or older have 4 times higher odds to acquire *P.knowlesi* infection compared to the control (Grigg, M.J., *et. al.*, 2014). This is also supported by Herdiana et all, whereby *P.knowlesi* cases are reported more among the adults (Herdiana, H. *et. al.*, 2016). Even asymptomatic cases that were detected by serology test, showed that seroprevalence of *P.Knowlesi* positivity was higher among those 15 years old and above (Fornace, K.M. *et. al.*, 2018). Age also has been reported to be strongly correlated with the risk of severe *P.knowlesi* infection with 56% of those with severe *P.knowlesi* infection are those more than 60 years old (Barber *et al.*, 2017). A retrospective review of malaria cases in Sabah showed that the overall median age of the patient with *P.knowlesi* was significantly higher than of patients infected with *P.vivax* and *P.falciparum* (William, T., *et al.*, 2013). A seroprevalence study that was conducted in four districts in Sabah, Malaysia showed that every increase of years by 10 would increase the odds of getting *P.knowlesi* by 33 % (Fornace, K.M., *et al.*, 2019). Male has a higher risk to acquire *P.knowlesi* infection with around 80- 90% of the proportion in each of the study population (Herdiana, H. *et. al.*, 2016; Fornace, K.M. *et. al.*, 2018; Grigg, M.J., *et. al.*, 2017; Goh, X.T. *et. al.*, 2013).

Occupation of being plantation workers and farming also shows an increased risk of acquiring *P.knowlesi* (Grigg, M.J., *et. al.*, 2017). Those working forest related has a higher percentage of cases of P.knowlesi cases (55%) compared to other jobs (Herdiana, H. *et. al.*, 2016). A seroprevalence study showed that a farm or plantation worker was positively associated with *P. knowlesi* seropositivity (Fornace, K.M. *et. al.*, 2018). Behavioral or habits like sleeping outside is an independent risk factor in acquiring *P.knowlesi* infection (Grigg, M.J., *et. al.*, 2017). Having open eaves and gaps in the wall of the house is known to have two times higher odds of getting *P.Knowlesi* infection (Grigg, M.J., *et. al.*, 2017). History of interactions with monkeys can be a factor to get *P.Knowlesi* infection (Barber, B.E. *et. al.*, 2013; Grigg, M.J., *et. al.*, 2017). A study showed a visit to the forest a month before the infection for any reason has found out to be the potential risk factor in acquiring *P.knowlesi* (Herdiana, H. *et. al.*, 2016). The cases in Kudat, Sabah was found to be in two family clusters.

They have not travelled into forested areas but the family has reported seeing macaques close to their homes (Barber, B.E. *et. al.*, 2013). Travelers who have visited the forest in the endemic country has been reported to carry this disease to their country of origin (Cramer, J.P., 2015). There is less chance of human to human transmission occurring with *P.knowlesi*. A study in Sandakan, Sabah (Goh, X.T. *et. al.*, 2013). *P.knowlesi* cases in Kudat, Sabah from 2009-2011 also showed a wide range of distribution among all age group with the youngest being 8 months old (Barber, B.E. *et. al.*, 2013). The wide age distribution and family clustering could be because the *P.knowlesi* vector might be biting humans close to or inside their' houses or there may be a potential human-to human transmission (Barber, B.E. *et. al.*, 2013). *P.knowlesi* has found out to be the common cause of malaria in adults and children in Kudat, Sabah (Barber, B.E. *et. al.*, 2011).

Bridget et all study showed that among the cases of *P.knowlesi* in Sabah from 2010-2011, the cases had a higher percentage of the previous history of infection with Malaria (5) compared to other *Plasmodium spp* infection. The cases also have higher cases with chronic diseases (Barber, B.E. *et. al.*, 2013). Those with G6PD deficiency seemed to have protective against *P.knowlesi* infection (Grigg, M.J., *et. al.*, 2017). Those with Duffy Blood Group also has been said to have resistance again *P.knowlesi* infection (Mason, S.J. *et. al.*, 1977).

Environmental factors

One of the driving factors of transmission of *P.knowlesi* to humans is due to ecological changes. Clearing vegetation has been shown to be associated with *P.knowlesi* infection (Fornace, K.M. *et. al.*, 2018; Grigg, M.J., *et. al.*, 2017). This suggests that ecological changes affect the human-vegetation interface. Land use and deforestation results in changes in ecological habitat affect the vector bionomics that favors increased blood feeding on humans (Grigg, M.J., *et. al.*, 2017). The higher historical forest was associated with a greater incidence of *P.knowlesi* infection (Fornace, K.M. *et. al.*, 2016). In another study conducted on seroprevalence in Sabah and Palawan showed that clearing areas within 500m of the house were associated with increased odds of *P.knowlesi* positivity (Fornace, K.M. *et. al.*, 2018).

P.knowlesi infection is seen in people living in rural forested and agricultural areas (Grigg, M.J., *et. al.*, 2017). Risk assessment has found as one who has a workplace near or in the forest has 7 times higher risk of infecting with malaria especially *P.knowlesi* (Herdiana, H. *et. al.*, 2016). A study on *P.knowlesi* risk map of cases using satellite imaging of Land-use and Land-cover (LULC) information showed a correlation (Sato, S. *et. al.*, 2019). The risk map showed that *P.knowlesi* cases in each village were affected by the LULC surrounding the village (Sato, S. *et. al.*, 2019). *P.knowlesi* seroprevalence was found to be higher in those living in low forest cover (Sato, S. *et. al.*, 2019). Besides that, seasonal variation has also shown as a significant factor for *P.knowlesi* infection, whereby maximum notification of cases occurs in June (William, T., *et al.*, 2013). The study in Kudat, Sabah showed that in 2009 the cases increased from March to July which in in 2009 it was from April to August. But in both years the number of reported cases peaked in May (Barber, B.E. *et. al.*, 2012). This same study showed that rainfall was strongly correlated with the number of *P.knowlesi* cases. The number of cases increased during the fifth month following the rainfall (Barber, B.E. *et. al.*, 2012).

Table 1: Summary of the findings

S.No.	Author	Year	Location	Study Design	Sample Size	Population	Individual factor	Environmental factor	Protective factor
1.	Grigg et al.	2017	Sabah	Case control	229	Malaysians	Adult, male, farmer, and palm oil plantation worker, sleeping outside,	living in rural forested and agricultural areas, Having open eaves and gaps in the wall of the house, history of Clearing vegetation	G6PD Deficiency, presence of young sparse forest and rice paddy around the house
2.	Herdiana et al	2016	Indonesia	Cross sectional	20	Indonesians	Adult, male, forest related job, visit the forest, Overnight staying in a forest	living in the rural forested area	-
3.	Fornace et al	2016	Kudat, Kota Marudu	Ecological study	329	Malaysians	-	Deforestation	-
4.	Fornace et al	2018	Kudat, Pulau Banggi, Palawan	Cross sectional	4	Malaysians, Philippians	Adult, male, farm or plantation worker	Land clearing, deforestation	-
5.	Barber et al	2017	Sabah	Cross sectional	146	Malaysians	Older adult	-	-
6.	Cramer	2015	USA (2), Taiwan, Sweden, Finland, Spain, Netherlands (2), Australia, New Zealand, France, Japan, Scotland, Germany (2)	Ecological study	15	International travellers	Travelling to the forest in an endemic country	-	2-

Continued…

S.No.	Author	Year	Location	Study Design	Sample Size	Population	Individual factor	Environmental factor	Protective factor
7.	Barber et al	2013	Sabah	Cross sectional	130	Malaysians	Previous history of malaria infection, history of chronic disease, history of seeing a monkey	-	-
8.	Sato et al	2019	Kudat	Cross sectional	107	Malaysians	-	Land clearing	-
9.	Xiang et al	2013	Sandakan	Cross sectional	42	Malaysians	A wide distribution of P.knowlesi in all age group$	-	-
10.	William et al	2013	Sabah	Cross sectional	Positive cases of P.Malariae/ P.knowlesi in Sabah#	Malaysians	-	Seasonal variation (in June)	-
11.	Barber et al	2012	Kudat	Cross sectional	339	Malaysians	A wide distribution of P.knowlesi in all age group*	Seasonal variation and rainfall	-
12.	Steven et al	1977	USA	Case study	3	Blacks, 2 Cree Indians and a white Australian	-	-	Duffy blood group individual
13.	Fornace et al	2019	Kudat, Kota Marudu, Pitas, Ranau	Cross sectional-seropreval	515	Malaysians	Age, sex, travel to forest areas, contact with macaque	Low forest cover	living in higher geographical elevation

#: from1992-2011 and total cases not mentioned in the article; *: Human-human transmission; $: presence of gametocyte in microscopic findings.

Meanwhile, *P.knowlesi* infections were found to be lower among those individuals residing at higher geographical elevations and individuals residing in houses less than 1 m from the ground (Fornace, K.M. *et. al.*, 2019). The presence of young sparse forest and rice paddy around the house has been associated with a decreased risk of acquiring *P.knowlesi* (Grigg, M.J., *et. al.*, 2017).

Discussion

The systematic review of 14 studies identified factors that are associated with *P.knowlesi* infection, and these factors were divided into host factors and environmental factors. These studies show that among other factors identified in the smaller, individual studies, these studies collectively identify age, sex, and occupation is host factors in the transmission of *P.knowlesi*. The environmental factors identified from these studies include seasonal variations as well as rainfall, while protective factors include geographical elevation.

The review noted that males, and especially older males, tend to have higher rates of *P.knowlesi* infections which could be explained by the demographic characteristics of the persons who tend to be more exposed to Anopheles spp. They tend to be those consistent with forest or plantation occupation, since men, especially older men, tend to be those that were more likely to have direct exposure to *P.knowlesi* vector. Besides this occupation, forest hunters, logging camp workers, jungle trekkers, military personnel on jungle training and veterinarians involved in research/ other activity also have the risk to get *P.knowlesi* infection (Roughton, S.A. *et. al.*, 2012). *P.knowlesi* has a more severe effect on the older population, since the severity of infection is related to the level of parasitaemia, increased inflammation, endothelial activation and microvascular function due to age-related changes in the ability to respond to the *P.knowlesi* parasite (Barber, B.E. *et. al.*, 2017).

These men would also be the ones who would have greater forest-related occupations such as the timber industries or oil palm plantation workers and would be more likely to live near forests instead of women and children (Grigg, M.J., *et. al.*, 2017). In addition, these occupations would have longer hours of work outdoors, leading to greater exposure to *P.knowlesi* vectors and their known peak outdoor feeding times between 6pm and 7 pm (Goh, X.T. *et. al.*, 2013). This increased duration outdoors is also important since *P.knowlesi* vectors as members of the *Leucophyrus anopheline* mosquito group would rest and feed outdoors, especially after dark (Abeyasinghe R. 2016).

Although forest occupations are a significant factor in *P.knowlesi* infections, those involved in agricultural occupations, such as farmers and palm oil plantation workers, would also have increasing exposure to *P.knowlesi* vectors since these occupations would be entering the forest and involved in extensive deforestation in order to produce arable agricultural land (Goh, X.T. *et. al.*, 2013). These encroachments to clear forest areas for agricultural activities would blend the distinction between forest, clearing, and habitation by creating irregular and fragmented edges between forest areas and cleared areas, reducing the distinction as well as the distance between the areas as noted in the Land-Use and Land-Clearing maps in areas of Sabah, Malaysia especially oil palm plantations close to the dense forest (Sato, S. *et. al.*, 2019).

This ragged patchwork of clearings with forest areas may increase the interaction of human, mosquito, and macaque populations between the two areas, creating a greater risk for infection especially when the distances between the edges are reduced and the distinction between the areas blurred and clearings around human habitation within 5KM of forest are associated with increased *P.knowlesi* infection (Fornace, K.M. *et. al.*, 2018). The importance of the increased human movement into these partially cleared areas would also increase exposure to the *P.knowlesi* reservoir or macaques, since macaques can be found close to human habitation. Macaques have been found to be highly adaptive and can be found close to human habitation.

In addition, *An.balabacensis* is known to exhibit "learning behaviour" with regards to host preferability as well as "habitat loyalty", returning to previous feeding sites. This may even take place after deforestation since *An.balabacensis* is a highly efficient vector, maintaining high levels of malaria in low population areas, and is related to *An.dirus*, a Mekong vector that is capable of adapting to deforestation (Barber, B.E. *et. al.*, 2012). Despite the efficiency of the vector, there is still little evidence of human-to-human transmission even though the development of gametocytes in humans for *P.knowlesi* has been confirmed since 2009. However, since more gametocytes are noted in microscopy of *P.falciparum* and *P.vivax* compared to *P.knowlesi*, one may infer that humans are getting infected by mosquitos that fed on macaques instead of feeding on humans (Goh, X.T. *et. al.*, 2013).

Cases of *P.knowlesi* malaria increase periodically with peaks around July and June every year (Barber, B.E. *et. al.*, 2013). This corresponds with the start of the rainy season in may since that is that is the period when the new rice planting season begins. *An.balabacensis* is known to breed in ground pools and areas of stagnant water in areas of clearing, such as oil plantations, rubber plantations, and fruit orchards. Even animal footprints can become a breeding area for these mosquitoes (Abeyasinghe R. 2016). *Anopheline* mosquitos are known to depend on rainfall for breeding sites, and *An.balabacensis* is shown to increase in numbers during months of greatest rainfall (Barber, B.E. *et. al.*, 2012) with a corresponding increase in *P.knowlesi* cases sometime later. One factor that has a negative association with *P.knowlesi* infection is geographical elevation. This could be due to the cooler climate, which in turn may reduce the reproduction of the vector due to the cooler pools of water which may have a larvicidal effect, reducing reproduction.

Although *P.knowlesi* infection occurs in other countries, the vectors in other countries have variations in species of vector dominance among Anopheles mosquitoes. Even animal reservoirs for the parasite may also be different for example long-tailed macaque and pig-tailed macaque is available on Borneo Island, while the banded leaf monkey is a reservoir in Peninsular Malaysia and Northern pig-tailed macaque in Myanmar. Factors associated with *P.knowlesi* in this review were identified, but not explored further in the respective studies.

Limitations

The limitations of this systematic review are a geographical limitation since the studies were mainly those from Borneo. Although *P.knowlesi* infection occurs in other countries, the vectors in other countries are other species of Anopheles mosquitoes, which may have subtle but significant differences from the vectors in Malaysia, generally and in Sabah, specifically. In addition, the animal reservoirs for the parasite may also be different, since only the long-tailed macaque and pig-tailed macaque are available on Borneo Island, while the banded leaf monkey is a reservoir in Peninsular Malaysia and Northern pig-tailed macaque in Myanmar. Another limitation is the low strength of evidence for the included studies in the systematic review. Factors associated with *P.knowlesi* were identified, but not explored further in the respective studies. However, they are among the evidence available for the review to form current recommendations.

Conclusion

Host factors such as sex and age as well as occupation as individual factors and environmental factors such as rainfall and geographic elevation have shown to have some association with *P.knowlesi* infection. The interaction between human movement into the forest and cleared areas adjacent to these dense forest areas needs to be explored further. Although humans can acquire this infection from macaques, human-to-human transfer in nature has not been established. This zoonotic malaria poses unique challenges that will need to be addressed if all forms of malaria are to be eliminated based on the sustainable developmental goal (SDG).

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