Review Research

RISK FACTORS FOR PLASMODIUM KNOWLESI IN SOUTHEAST ASIA : A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Plasmodium knowlesi zoonotic malaria has been identified in Borneo Malaysia in 2004, and has led to an increase in the number of cases throughout Southeast Asia. Many factors have contributed to increasing pattern. Therefore, this systematic review aims to identify risk factors for Plasmodium knowlesi infection that can aid in predicting and controlling the infection. **Methods:** Systematic search on articles related to risk factors of Plasmodium knowlesi infection was conducted using three databases namely PubMed, Scopus and Science direct. All the articles from year 2015 till May 2019 were selected. **Results:** A total of three articles were included in this review based on the study protocol. Three common risk factors for Plasmodium knowlesi infection was in identify mainly involved sociodemographic, work-related and behavioural factors. **Conclusion:** Risk factors for P. Knowlesi ranges not only from individual and community socidemographic background but also by environmental and geographical determinants. The inconsistency of the result was due to the variability and limitations of the studies itself. The research on P. Knowlesi, should be conducted with larger participants and longer length of follow up.

Keywords: Plasmodium, P.Knowlesi, risk factors, Asia

Introduction:

Plasmodium knowlesi (P.knowlesi) is a primate malaria parasite commonly found in Southeast Asia (Perkin & Schall, 2002). In Malaysia, P. knowlesi is consider emerging infectious disease related to zoonotic human malaria. It causes zoonotic malaria in long-tailed macaques (Macaca fascicularis). Southeast Asia(SEA) reported most of the cases with macaque as a hosts.

P. knowlesi zoonotic malaria has been identified in Borneo Malaysia in 2004, and has led to an increase in the number of cases of P. knowlesi throughout SEA (Singth et al, 2004) Infections can cause severe illness and death although most people infected with P. knowlesi respond to treatment (Ahmed et al, 2014). P.knowlesi malaria is potentially life-threatening due to the special features of the zoonotic malaria, that is, 1) having a much shorter incubation period of 24 hours as compared to other type of human malaria species, 2) having atypical presentation that has common symptoms shared by many other viral diseases such as dengue fever, 3) fast deteriorating once clinically symptomatic due to hyperparasitaemia found in macaque when infecting human as the macaque are their natural hosts who has developed natural immunity towards the parasite and have not suffer disease, 4) the zoonotic malaria is capable to cause acute multiple organs failure as the parasites invaded human body. People who are infested with P.knowlesi are usually died of hepatorenal syndrome and septicaemia (Cox-Singh et. al, 2010).

The first cases of naturally acquired human infection described in Peninsular Malaysia in 1965. The spill-over infections from the traditional monkey-vector transmission cycle presumed to be infrequent (Shearer et al, 2016). The majority of cases are from Eastern Malaysia, with increasing trend of the notifications (Grigg et al. 2014). Since year 2001, P. Knowlesi has become an emerging vector-borne disease in Malaysia, especially Sabah, Sarawak at east Malaysia, and Pahang, Kelantan of West Malaysia. In Sabah, a marked, rapid increase in the number of P. knowlesi cases reported recently beginning in the southwest and progressing to north-easterly.[7] (William, Jelip et al. 2014). Public health microscopy notifications for P. knowlesi in Sabah (including those reported as P. malariae) have increased from around 2% (59/2741) of all malaria cases in 2004, to 35% (703/1936) in 2011 and, recently, to 62% in 2013 (996/1606) (Sabah Department of Health). In Sarawak, P. knowlesi or P. malariae microscopy notifications were 14.3% (1731/12 082) of all malaria cases between 2000 and 2006 (Cox-Singh & Singh, 2008), increasing to 41% (897/2189) in 2009 (Singh & Daneshvar, 2010) and to 73% (737/1004) in 2013.

P knowlesi cases have now been stated from all countries in SEA except in Laos (Wesolowski et al, 2015). It is encompass the range of geographical area for the natural macaque hosts (Macaca fascicularis and Macaca nemestrina) and Anopheles leucosphyrus group vectors (Cox-Singh & Singh, 2008). Since 2004, some sporadic cases of P. knowlesi human malaria have also been reported in several Asian countries including

Singapore, Brunei, Indonesia, Thailand, Cambodia, Myanmar Vietnam, India, China and the Philippines (Zhu et al, 2006)

Till date, there is no background data to gauge the actual prevalence unless country wide retrospective-cohort study is done. If this is true, a well-organized one-health team-based approach is urgently called for to face this challenge, as the epidemiology and risk factors for P.knowlesi are totally different from all the other plasmodium species. Therefore, this study aim to systematically collect the evidence of possible risk factors that contributes to the transmission and infection of P.knowlesi in SEA.

METHODS

Systematic search related to relevant articles from four major search engines using Boolean search strategy, search engines including PubMed (National Library of Medicine Bethesda 1996), Scopus, Science Direct (Elsevier 1997), retrieving all articles published from year 2015 until May 2019. PRISMA checklist 2009 is used to describe the workflow of articles search for this study. The keywords used to search for the articles are Risk factor OR Predictor OR Explantory AND Plasmodium Knowlesi OR P.knowlesia OR Simian Malaria OR Zoonotic Malaria AND Malaysia OR Southeast Asia OR SEA OR ASEAN.

Inclusion criteria for the article search including: (1) full text, primary research articles on risk factor of Plasmodium knowlesia infection; 2) reported at least one risk factor of Plasmodium knowlesia infection and; (3) articles published from year 2015 – May 2019. Exclusion criteria set were: (1) reviewed articles of no original research work empirical data; (2) entomology with no association to risk factors; (3) Knowledge, Attitude, Practice studies; (4) clinical treatment; (5) pharmaceutical study and; (6) risk factors for other Plamodium infection

The articles obtained from the keyword search were first screened by titles to exclude totally irrelevant articles, then abstracts of the articles to look for PICO criteria. When full texts are retrieved, it was assessed for relevance to include our inclusion and exclusion criteria. In total, there is a total of 114 articles retrieved based on Boolean search strategy. 46 articles from Pubmed, 53 articles from science direct and another 15 articles from Scopus. After excluding 10 articles for duplication, 104 are screen by titles and abstract yielding 32 articles accepted for further screening. 29 of full-text articles were excluded due no risk factors (1), targeted specific population only (1), geographical study (5), diagnostic investigation (8) and mixed malarial infection (14). Final full articles reviewed and proceed for qualitative syntheses are 3 articles (Figure 1).

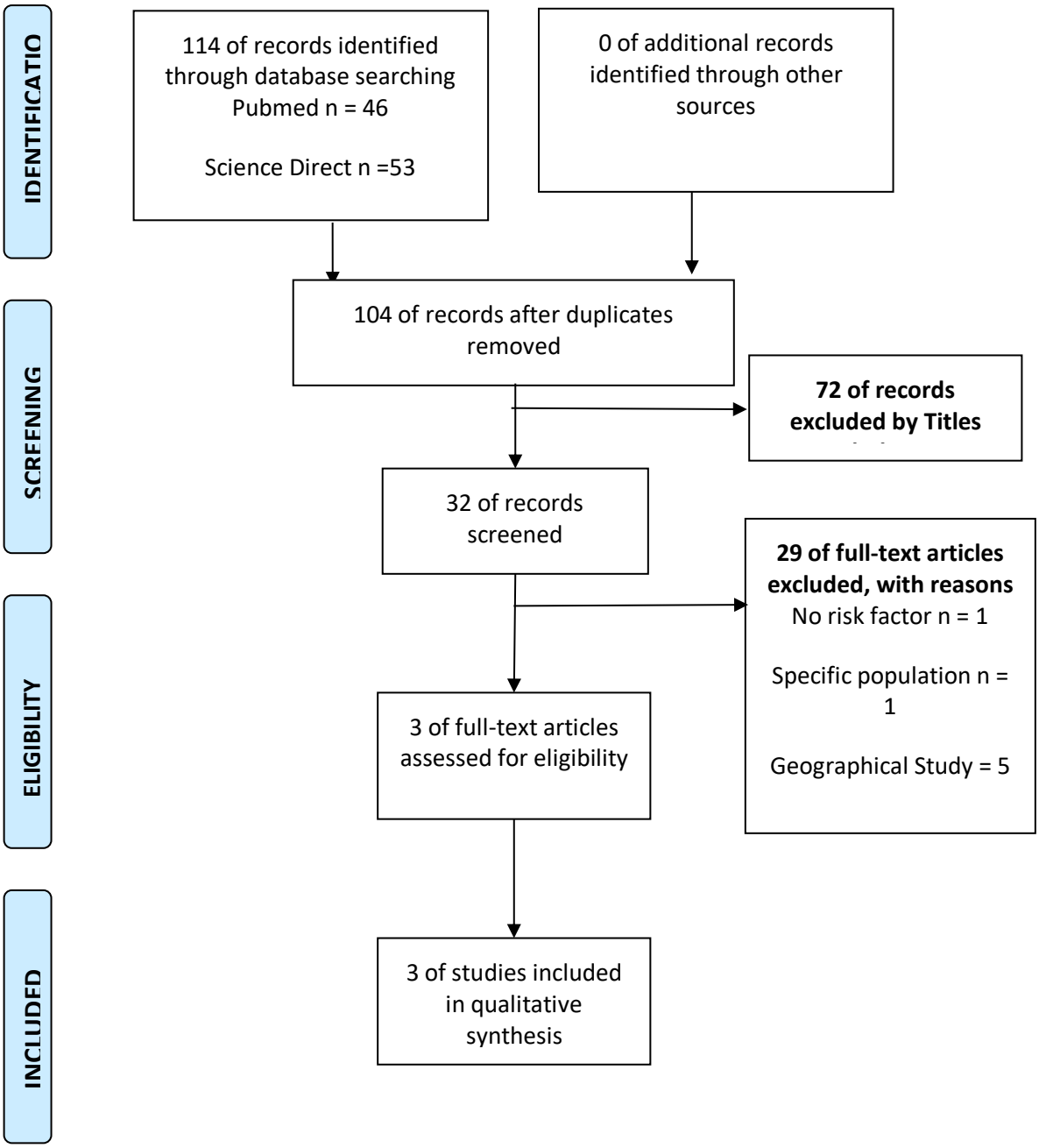

Figure 1: studies selection related to P.Knowles

Results:

A summary table of all the included articles for analysis (Table 1), there was a total of 3 articles, which consist of one cross sectional and two case control studies. The articles are mostly from Sabah, Malaysia and Philippines. Across the articles, the common risk factors for P. knowlesi infection are age, gender, occupation, contact with macaque, behavioural factor while protective factors are children, use of insecticide, house at ground level, presence of sparse forest & paddy field near the house. The quality of the studies which were assessed by using *Newcastle-Ottawa Scale* ranged from 6 to 8 stars. Total of 2 articles were given good quality and one with moderate quality of evidence as shown in Table 2.

Table 1: Summary of included studies

Author & Year	Country	Population	Length of study	Effect Measure	Risk Factor	OR (95% CI)
Fornace,2019	Sabah, Malaysia	Kudat, Kota Marudu, Pitas, & Ranau, Sabah 2849 household in 180 village N = 10,100	3 months (Sept – Dec 2015)	OR	Age Male Contact with macaque Forest activities Irrigated farming (300m radius) Pulpwood plantation (3000m radius) Oil palm (<3000m radius) Use of insecticide House at ground level Intact forest	1.33 (1.27, 1.39) 1.25 (1.04,1.48) 1.42 (1.17,1.71) 1.47 (1.65, 2.37) 1.17 (1.07, 1.28) 1.15 (1.07,1.24) 1.10 (1.01,1.20) 0.77 (0.63.0.91) 0.76 (0.63,0.91) 0.86 (0.75,0.96)
Fornace,2018	Sabah, Malaysia & Bacungan, Philiphine	a) Matunggong & Limbuat, Sabah N = 172 cases & 1957 control b)Bacungan, Philipinie N = 6 cases & 546 control	5 months (Sept 14 – Jan 15)	OR	15 – 45 years 45 – 60 years > 60 years Farm or plantation work Forest cover (1000m radius) Proportion of cleared /open area (500m radius)	2.05 (1.30,3.22) 2.94 (1.70,5.11) 2.46 (1.32,4.58) 1.63 (1.07,2.48) 2.40 (1.29,4.46) 2.14 (1.35,3.40)
Grigg,2017	Sabah, Malaysia	Kudat & Kota Marudu, Sabah N = 229 cases & 683 control	2 months (Dec 2014 – Jan 2015)	OR	Children < 15 years Adult >15 years Male Contact with macaque Farm or plantation work Farming Palm oil Clearing Vegetation Sleeping outside Travel	0.29 (0.18,0.47) 3.81 (2.31,6.28) 4.02 (2.83,5.72) 4.06 (2.71,6.08) 3.08 (2.20,4.29) 2.66 (1.82,3.88) 3.22 (1.72,5.61) 3.49 (2.44,5.00) 6.63 (3.47,12.69)

					Having long grass around house Having open eaves or gap in walls G6PD deficiency Lived in village past 6 months Presence of young sparse forest Residual Insecticide Presence of paddy field	2.66 (1.85,3.81) 2.13 (1.48,3.07) 2.17 (1.50, 3.14) 0.11 (0.02,0.46) 0.46 (0.26,0.88) 0.44 (0.30,0.64) 0.77 (0.54,1.09) 0.51 (0.19,1.36)

Table 2: Newcastle Ottawa Quality Assessment Scale

No	Study	Selection				Comparability		Outcome		Quality score
		Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	The study controls for the most important factor	The study control for any additional factor	Assessment of the outcome	Statistical test	
1.	Fornace 2019	*	*	*	*	*		**	*	8
2.	Fornace 2018	*			*	*		**	*	6
3.	Grigg 2017	*	*	*	**	*		**	*	8

Discussion

The main risk factors for P. Knowlesi malaria infection for countries under SEA region can be divided into three big groups which is the socio-demographic background, work related and behavioural factors. The finding of a higher risk of infection in adult males and age between 15 to 45 years old are consistent with other studies. According to Fornace et al. (2016), risk of getting P.Knowlesi in certain area like Pulau Banggi, Kudat Sabah is the highest with aOR 10.83 (95%CI: 4.5-26.1) compared to other studied location such as Palawan, Filipina and other part of Sabah. Due to the job nature's demand, risk factor like forest exposure are quite unavoidable. Forest-based work such as: logging, clearing vegetation, palm oil plantation and rubber tapping is usually done by men. Furthermore, the jobs mention requires workers to stay during the night in the forestry. Therefore, the job natures are strongly associated with P. Knowlesi infection and this leads to adult men are at high risk for infection.

Since forest workers are higher risk getting the P. knowlesi malaria therefore the efforts for mass screening needs to focus among them rather than targeting villagers. The screening radius may reduced to less than 100m even though the WHO recommended for 1-2km (Herdiana et al. 2016). The collaboration with other agencies such as forestry, agriculture and local partner (logging site supervisor, farm owners) should be enhance in engaging the forest workers for malaria prevention and control activities. The activities may include health education in promoting health seeking behaviours. The distribution of ITN should include among them as the distribution by local goverment mainly involve residence area and this product not available to purchase. ITN used have a rapid treatment by providing personal protection to humans with maximal estimated reductions in human (Natsuko et al. 2014). For

job require overnight stays at the forest far from village or subdistrict, a mobile surveilance system should be developed and enhanced for monitoring the forest workers. The data collected are useful for future planning in malaria elimination.

Behavioural risk factors are related to the individual or the local community's culture and lifestyle. Examples included in the study are sleeping outside, travel, long grass around houses, open eaves/gaps in walls and house at ground level. By providing adequate knowledge and awareness regarding mode of transmission and risk factors for P. Knowlesi to the local community, it can helps with the transition of risk behaviour towards protective behaviour.

In African countries, the prevalence of risk factors for malaria among households with clean water to be less. House with thatch and stick/mud roof and earth/local dung plaster floor found to be higher with malaria through rapid test. Therefore, spraying anti-malaria to the house able to reduce the risk of malaria transmission. Furthermore, the housing condition, source of water and its distance, gender, and ages in the households were identified in order to have two-way interaction effects (Ayele et al 2012). Such pattern of risk factors are quite different from the risk factors for specific zoonotic malaria like P. Knowlesi where's it highly linked to the patient's nature of job and history of exposure to jungle or its natural reservoir.

Conclusion

Risk factors for P. Knowlesi ranges not only from individual and community sociodemographic background but also by environmental and geographical determinants. The inconsistency of the result was due to the variability and limitations of the studies itself. However, there are still comparable prospect on the risk factors for P. Knowlesi which can influence on health related behavioural modification. For future research on P. Knowlesi, it should be conducted with larger participants and longer length of follow up with provided numbers for cases group and control group to produce quality results thus could generate significant result for meta-analysis. Intevention study in future may provide a significant findings in reducing the burden of P. Knowlesi malaria. The high burden of P. knowlesi in SEA needs attention for further investigation related to its epidemiology and specific risk factors. P. knowlesi malaria transmission are the new challenge in endemic area in achieving malaria elimination.

Conflicts of Interest:

The author declare no conflicts of interest.

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