PLASMODIUM KNOWLESI AND FOREST GOERS: WHAT'S NEXT?

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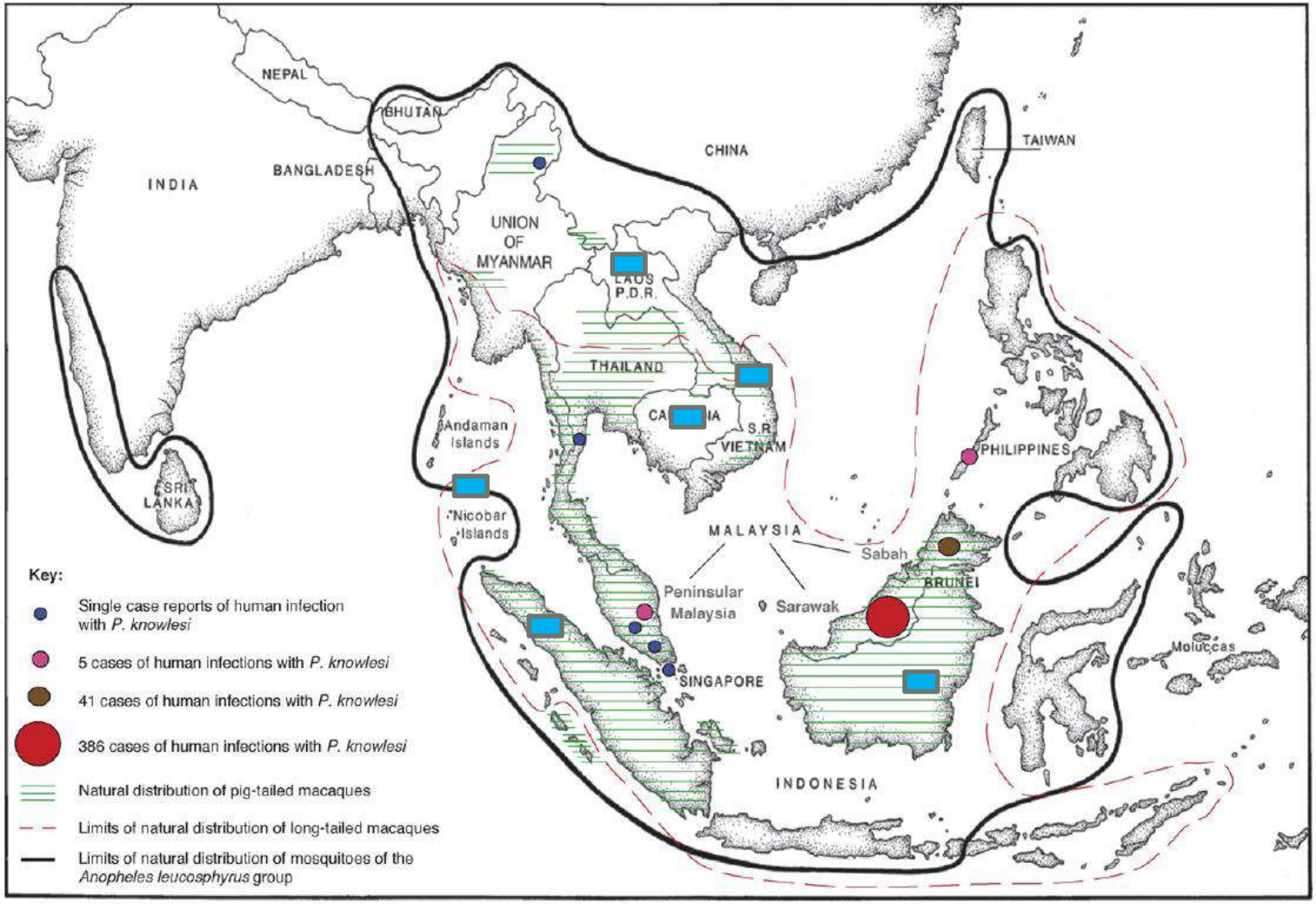
Introduction

- ***Plasmodium knowlesi*- simian malaria parasite affecting humans – in Southeast Asia**
- **Predominant species forming 89% of the cases in Malaysia in 2018 – 4131 cases**
- **Malaysia is in the pipeline for malaria elimination**
- **What about other species?**

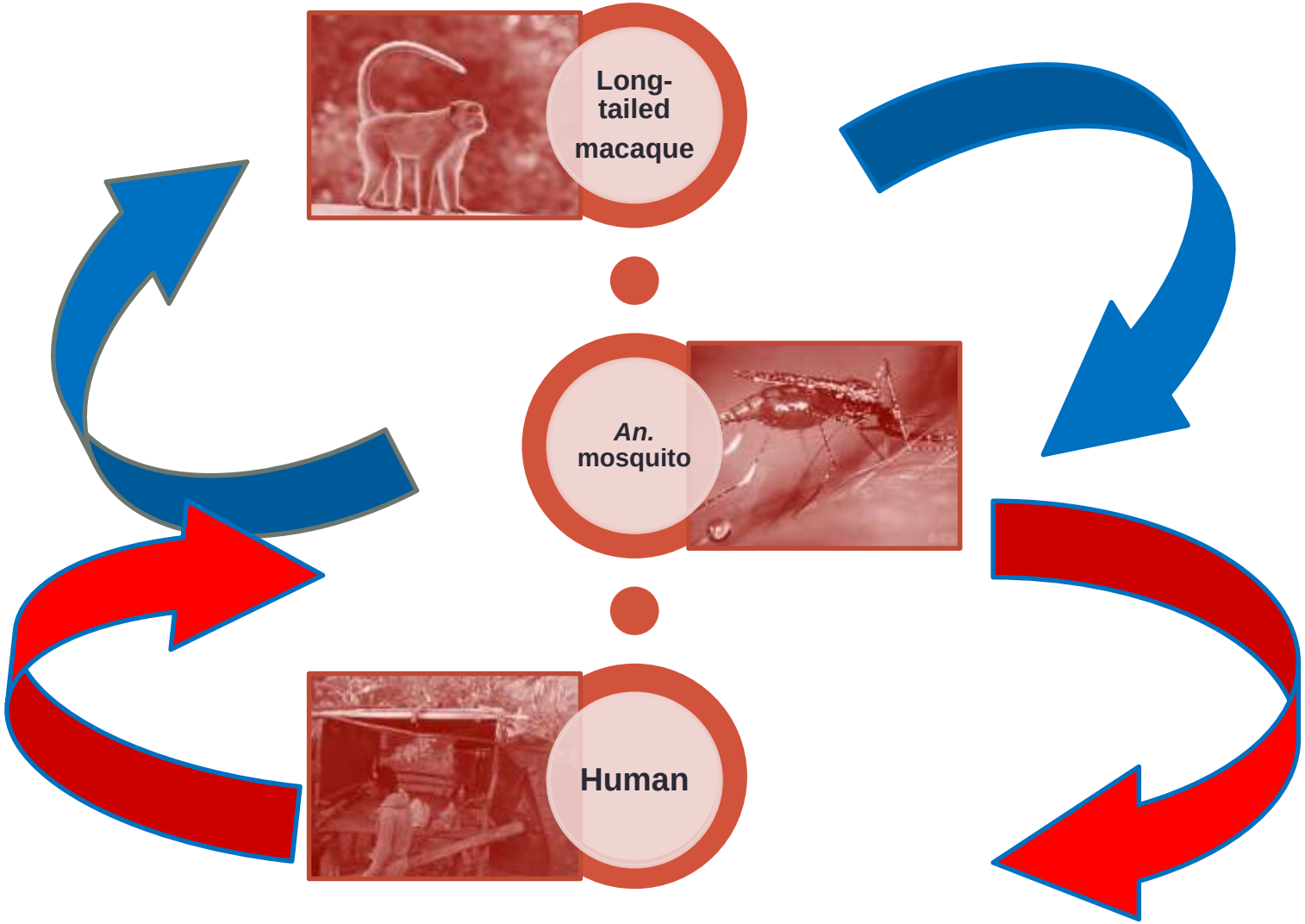
Distribution of Leucosphyrus group of *Anopheles M*osquitoes, Macaques, Malaria



TRENDS in Parasitology

Cox-Singh and B. Singh 2008 Trends in Parasitology

Man: Monkey: Mosquito



Collection of Mosquitoes

Plasmodium cynomolgi

Laboratory infection in 1960s

1965 First natural infection in human American surveyor

Tracing History of *P. knowlesi* Vectors

Wharton & Eyles 1961

An. hackeri

Coastal area of Selangor (biting only monkeys)

1961

1964

Wharton et al 1964

***An. latens* (*P.i*)**

Ulu Lui

***An. introlatus* (*P.cy*, *P. fi*) Ulu Gombak**

Selangor

1965

Cheong et al 1965

***An. cracens* (P.i, P.cy)**

Perlis

Current Results on Vectors of Pk

2006

Vythilingam *et al* 2006

Tan et al 2008

An. latens

Kapit

2008

Kuala Lipis

Vythilingam et al 2008

Jiram et al 2012

An. cracens

2014

Vythilingam et al 2014

An. introlatus

H. Selangor

2015

Kudat, Sabah

Wong et al 2015

Chua et al 2017

Chua et al 2019

Hawkes et al 2019

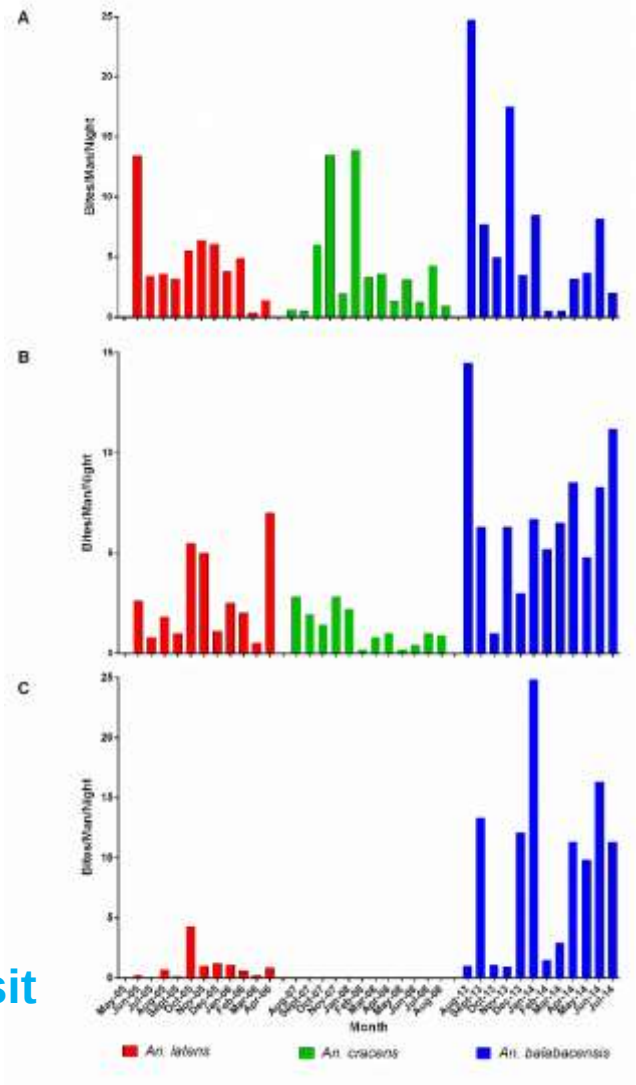
An. balabacensis

Summary of Longitudinal Studies

Farm

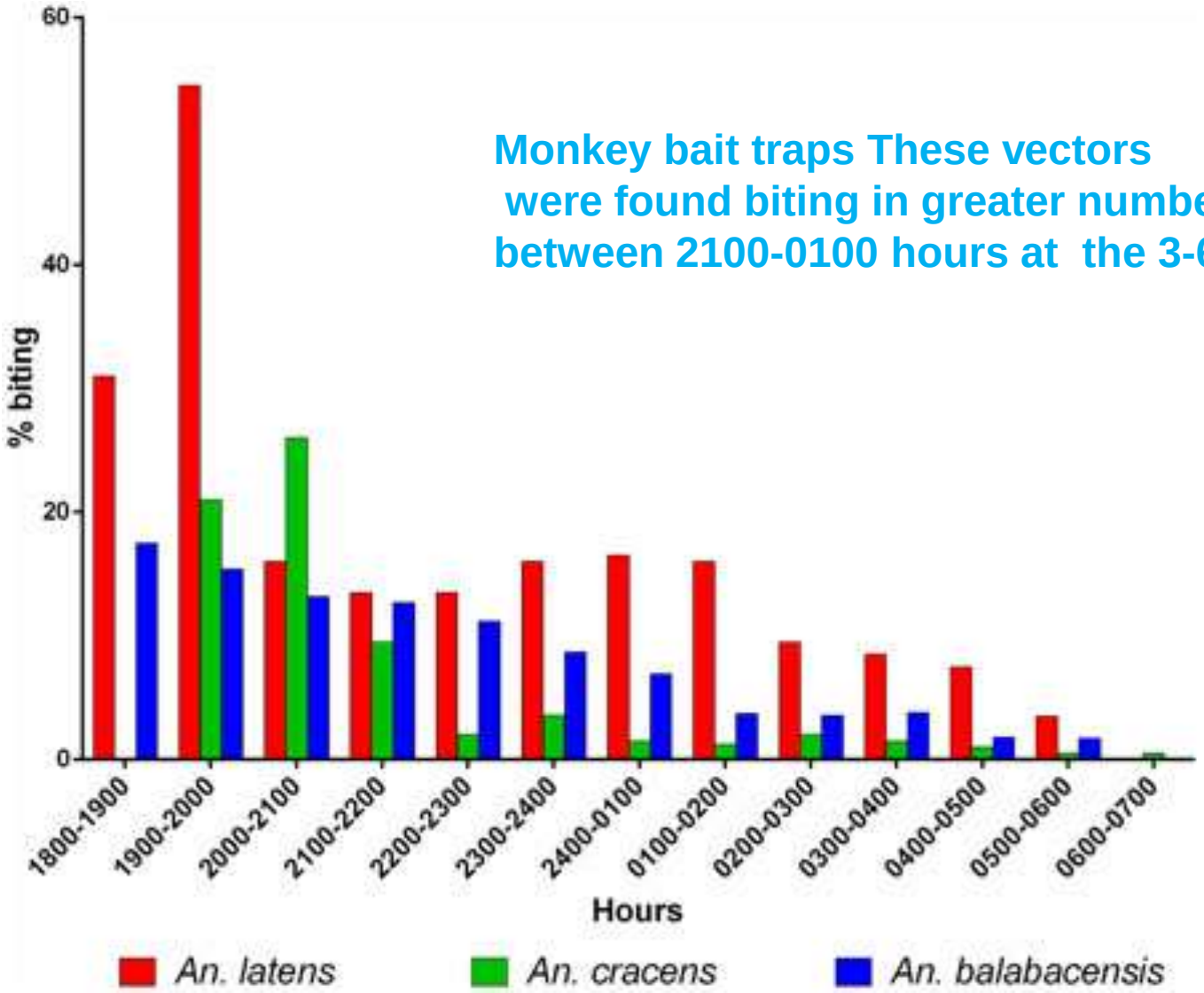
Forest

Village



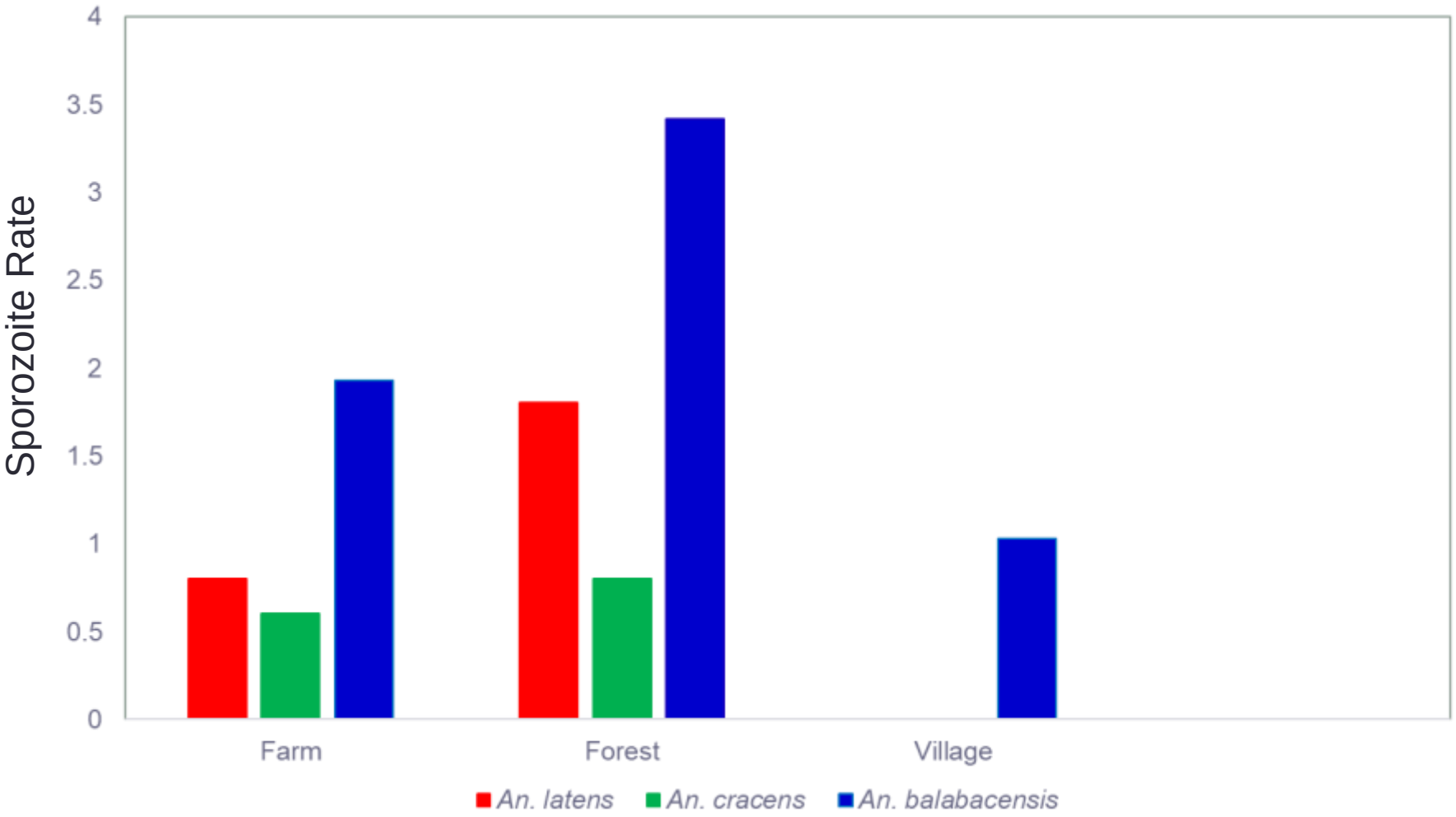
Vythilingam et al 2016 Parasit
Wong et al 2015 PLoS NTD

Biting Times of 3 Predominant Vectors



Monkey bait traps These vectors were found biting in greater numbers between 2100-0100 hours at the 3-6 meters

Sporozoite Rates



Anophelines Caught Indoors/Outdoors Case and Control Houses

Anopheles sp	Indoors		Outdoors	
	Case	Control	Case	Control
An. balabacensis	**18**	**16**	**374**	**233**
An. maculatus	1	1	12	35
An. *barbumbrosus*	2	0	24	11
An. donaldi	1	0	7	26

10 positive for simian malaria but none for *Pk*

Manin et al PLoS NTD 2016

Vectors Other than *An*. Leucosphyrus Group?

- ***An. donaldi*** and ***An. watsonii:*** **oocyst present**
- PCR: ***Plasmodium* positive** but could not be speciated
  ***An. kochi* – in monkey bait traps – none positive**
- **Andaman & Nicober Is**: ***An. sundaicus* – pooled positive Pk (PCR) (Vidhya et al (2019 EID)**
- **Hawkes et al. (2019) in Sabah found *An. donaldi* positive for DNA of *P. knowlesi* (n=2), *P. cynomologi* (n=1) and an unknown *Plasmodium* species (n=1)**
- **Gold standard to dissect mosquitoes and examine midgut and salivary glands: positives follow up with PCR**

Number of Salivary Glands of *Anopheles* Infected with Parasites

Parasite Species	Salivary Glands Positive
Pk	8
Pcy	14
Pin	20
Pct	5
Pk + Pcy	3
Pk + Pin	4
Pcy+ Pfi	1
Pin + Pcy	8
Pin + Pfi	4
Pk + Pcy + Pin	4
Pin + Pcy + Pfi	1
Pk + Pct + Pcy +Pi	1

Studies conducted from 2005 onwards

Vectors of *P. knowlesi* in Vietnam

Table 2 Summary of *Plasmodium* spp. infections in *Anopheles dirus*

Infection	*Plasmodium* spp.	No. of mosquitoes infected
Single (53)	Pf	4
	Pv	27
	Pk	4
	Pct	7
	Pcy	6
	Pin	5
Double (19)	Pf, Pv	3
	Pf, Pin	1
	Pv, Pk	7
	Pv, Pcy	3
	Pv, Pin	3
	Pk, Pin	2
Triple (6)	Pf, Pv, Pin	1
	Pv, Pk, Pcy	1
	Pv, Pk, Pin	2
	Pv, Pct, Pin	1
	Pk, Pct, Pin	1
Quadruple	Pv, Pct, Pcy, Pin	1
No. of PCR-positive		79
No. of PCR-negative		4
Total no. of examined sporozoite-positive		83

Pf = *P. falciparum*, Pv = *P. vivax*, Pk = *P. knowlesi*, Pct = *P. coatneyi*, Pcy = *P. cynomolgi*, Pin = *P. inui*

Maeno et al 2015

Results of Macaque Survey

Sarawak

P. fieldi 4%

P. cynomolgi 56%

P. coatneyi 66%

Selangor

P. knowlesi 60%

P. coatneyi 45.7%

P. cynomolgi 51.4 %

Lee et al 2011 Plos Pathogen

Akter et al 2015 Malaria J

Table 1 Malaria parasite infections in long-tailed macaques by location

Infection	*Plasmodium* species	Number of long-tailed macaques infected							
		Laos	Singapore	Vanny, Cambodia	Batangas, Philippines	Zamboanga, Philippines	Southern Sumatra	Bintan Island	Total
Single	Pk	1							1
	Pcy	28	23	24	2	1	39	9	126
	Pct			7		1		1	9
	Pin		2	1		2	1	2	8
	Pfi		1						1
Double	Pcy, Pin		1	2			9	2	15
	Pin, Pfi		1						1
	Pct, Pfi	1	1						2
	Pcy, Pfi			1				1	2
	Pct, Pcy		1		1				1
	Pin, Pct			9					9
Triple	Pcy, Pin, Pfi		1					1	2
Total *Plasmodium*-positive		30	31	44	3	4	49	16	177 (64.1 %)
Total *Plasmodium*-negative		14	9	10	25	36	1	4	99 (35.9 %)
Total number of macaques		44	40	54	28	40	50	20	276 (100 %)

Pk P. knowlesi, Pcy P. cynomolgi, Pin P. inui, Pct P. coatneyi, Pfi P. fieldi

Zhang et al 2016 Malaria J

Plasmodium cynomolgi

The Journal of Infectious Diseases
MAJOR ARTICLE

Asymptomatic Natural Human Infections With the Simian Malaria Parasites *Plasmodium cynomolgi* and *Plasmodium knowlesi*

Mallika Imwong,[1,2] Wasassanan Madmanee,[2] Kanokon Suwannasin,[2] Chanon Kunasol,[2] Thomas J. Peto,[2,3] Rupam Tripura,[2,3] Lorenz von Seidlein,[2,3] Chea Nguon,[4] Chan Davoeung,[5] Nicholas P. J. Day,[1,2] Arjen M. Dondorp,[1,2] and Nicholas J. White[2,3]

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(See the Editorial Commentary by Garry on pages 511–3.)

Background. In Southeast Asia, *Plasmodium knowlesi*, a parasite of long-tailed macaques (*Macaca fascicularis*), is an important cause of human malaria. *Plasmodium cynomolgi* also commonly infects these monkeys, but only one naturally acquired symptomatic human case has been reported previously.

Methods. Malariometric studies involving 5422 subjects (aged 6 months to 65 years) were conducted in 23 villages in Pailin and Battambang, western Cambodia. Parasite detection and genotyping was conducted on blood samples, using high-volum

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First case of a naturally acquired human infection with *Plasmodium cynomolgi*

Thuy H Ta, Shamilah Hisam, Marta Lanza, Adela I Jiram, NorParina Ismail & José M Rubio

Malaria Journal 13, Article number: 68 (2014) | Cite this article

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« Previous Article August 2018 Volume 73, Supplement, Page 68 Next Article »

Naturally acquired human infections with the simian malaria parasite, Plasmodium cynomolgi, in Sarawak, Malaysian Borneo

B. Singh[1] K.A. Kadir[1] T.H. Hu[1] T.N. Raja[1] D.S. Mohamed[1] L.W. Lin[1] K.C. Hi[2]

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DOI: https://doi.org/10.1016/j.ijid.2018.04.2001 | Check for updates

The Journal of Infectious Diseases
BRIEF REPORT

Natural Human Infections With *Plasmodium cynomolgi* and Other Malaria Species in an Elimination Setting in Sabah, Malaysia

Lynn Grignard,[1] Sonal Shah,[1] Tock H. Chen,[1] Timothy William,[1,2] Chris J. Drakeley,[1] and Kimberly M. Fornace[1,2]

[1]Faculty of Infectious and Tropical Diseases, and [2]Centre for Climate Change and Planetary Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah; [4]Infectious Diseases Society Sabah-Menzies School of Health Research Clinical Research Unit, and [5]Gleneagles Hospital, Kota Kinabalu, Malaysia

To determine the presence and species composition of malaria infections, we screened a subset of samples collected during a cross-sectional survey in Northern Sabah, Malaysia using highly sensitive molecular techniques. Results identified 54 asymp-

people in closer contact with long-tailed and pig-tailed macaque reservoirs (*Macaca fascicularis* and *M. nemestrina*) [4]. These macaque species also carry other *Plasmodium* species, including the zoonotic species *P. cynomolgi* [5]. While human infection with *P. cynomolgi* had been demonstrated in laboratory studies, the first natural human infection with *P. cynomolgi* was identified in West Malaysia in 2011 [6]. A more recent study identified mixed *P. cynomolgi* and *P. knowlesi* infections in 5 clinical cases in Sarawak in Malaysian Borneo [7]. Subsequent studies identified multiple asymptomatic human infections with *P. cynomolgi* in Cambodia in 2015; however, no asymptomatic human infections have been described in Malaysia [8].

Within Sabah, high prevalences of *P. cynomolgi* and coinfections with *P. knowlesi* and *P. cynomolgi* have been described in both macaque and mosquito populations. In Northern Sabah, entomological investigations of the main

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Volume 25, Number 10—October 2019

Dispatch

Plasmodium cynomolgi as Cause of Malaria in Tourist to Southeast Asia, 2018

Gitte N. Hartmeyer, Christen R. Stensvold, Thilde Fabricius, Ea S. Marmolin, Silje V. Hoegh, Henrik V. Nielsen, Michael Kemp, and Lasse S. Vestergaard

Author affiliations: Odense University Hospital, Odense, Denmark (G.N. Hartmeyer, T. Fabricius, S.V. Hoegh, M. Kemp); Statens Serum Institut, Copenhagen, Denmark (C.R. Stensvold, H.V. Nielsen, L.S. Vestergaard); Sygehus Lillebælt, Vejle, Denmark (E.S. Marmolin)

Cite This Article

On This Page

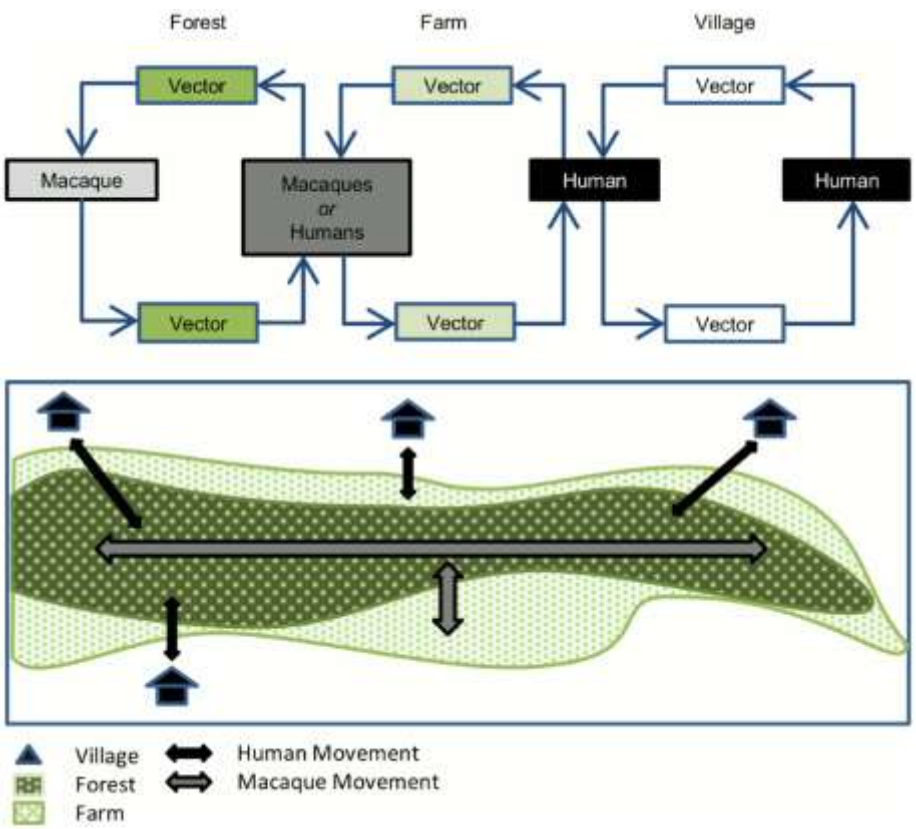
The Study

Conclusions

Cite This Article

Hoosen and Shaw 2011 *Travel Med.Infect Dis.*; Mali et al. 2008 *MMWR Surveill Summ* ; Kantele et al. 2008 *Emerg Infect. Dis.;* Bronner et al. 2009 *Malar. J.;* Tang et al. 2010 *Malar. J.;* Berry et al. 2011 *Am. J. Trop.Med. Hyg.;* Figtree et al. 2010 *Emerg Infect Dis.*

Movement of Man, Macaques, Mosquitoes



Imai et al PLOS NTD 2014 July

Conclusions

- **With malaria elimination, humans may become less immune to malaria. Thus become more susceptible to *Pk* and other simian malaria**
- **Macaques are infected with *P. inui* and *P. cynomolgi***
- **Mosquitoes also infected with *P. inui* and *P. cynomolgi***
- **Mosquitoes biting early – outdoors- IRS & ITNS will not be effective**
- **It is pertinent to screen people living in high risk areas not just for *Pk* but other simian malaria as well**
- ***Pf* and *Pv* non human primates - jumped the barrier**
- **New tools are required to control the vectors**

Acknowledgements

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MOSTI, MOE, University of Malaya, HIR
INT: London School of Hygiene
and Tropical Medicine

2005-
2006

2007-2008

2013-2017

2019-2022

Thank You

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Leucosphyrus Group: 3 Subgropus

Subgroup	Complex	Species	Distribution
Leucosphyrus	Leucosphyrus	*An. leucosphyrus*	Indonesia, Sumatra
		An. latens	Indo, Mal, Thai
		An. introlatus	Indo, W Mal, Thai
		An. balabacensis	Brunei, Indo, E Mal, Phil
		An. baisasi	Phil
	Dirus	*An. dirus*	Cam, Viet, Laos, Thai, Ch
		An. cracens	Indo, W Mal, Thai
		An. scanloni	Thai
		An. baimaii	BD, In, Thai, My, Ch
		An. elegans	SW In
		An. takasagoensis	Ch, Tw
		An. nemophilous	W Mal, Thai
		An. mirans	In, SL

Leucosphyrus Group - Contd

Subgroup	Species	Distribution
Hackeri	*An. hackeri*	Mal, Phil, Thai
	An. pujutensis	Indo, Mal, Thai
	An. recens	Indo
	An. sulawesi	Indo
Riparis	*An. riparis*	Phil
	An. cristatus	Phil
	An. macarthuri	Mal, Thai