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Plasmodium knowlesi: Old Story but New Fact in Southeast Asia

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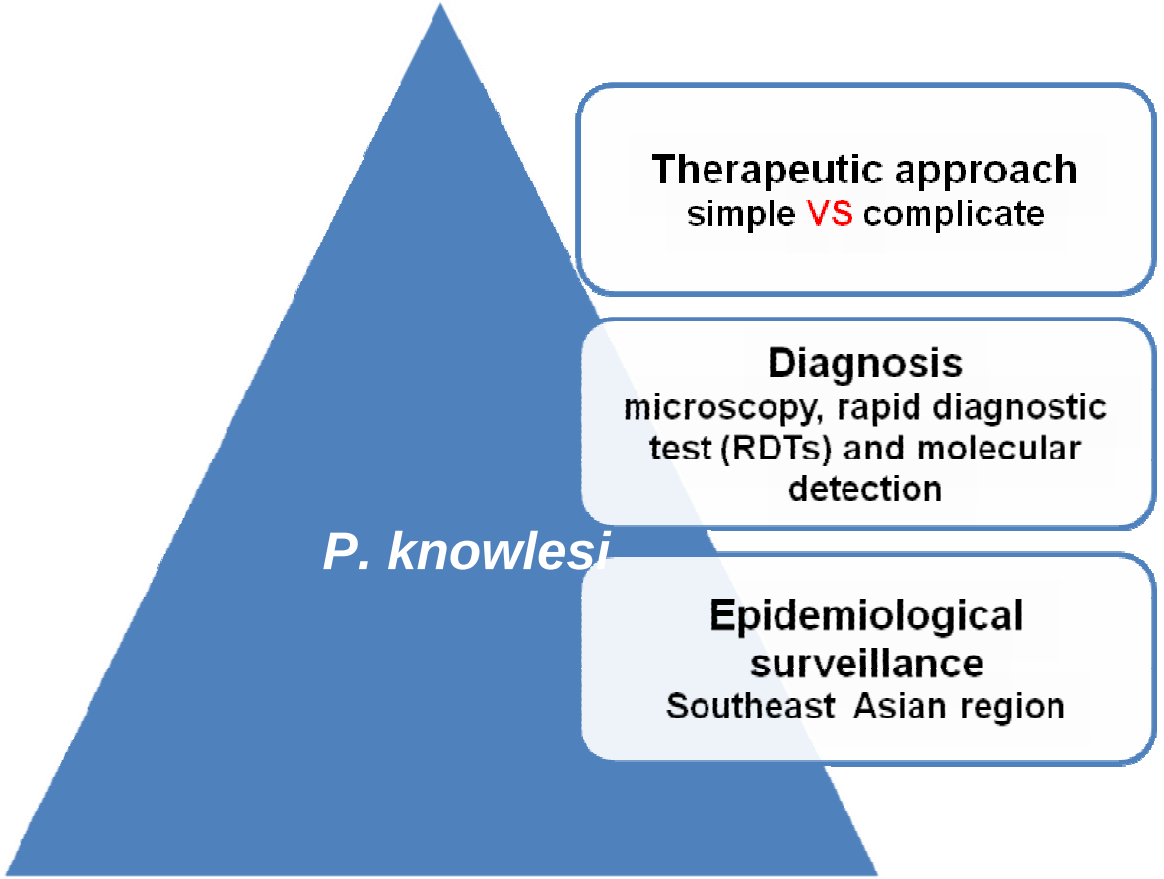
Knowlesi malaria: When, Where, Why, and How?



A fifth *Plasmodium*, human malaria parasite, monkey malaria, primate malaria, simian malaria, zoonotic knowlesi malaria, human knowlesi malaria, and a novel malaria

Plasmodium knowlesi

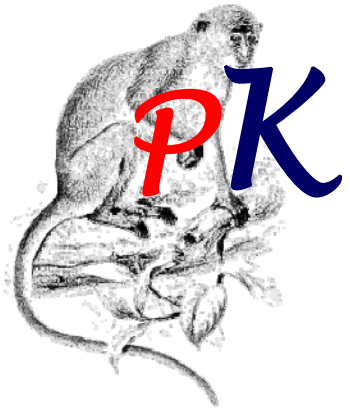
1931: was first isolated from a long-tailed macaque imported to India from Singapore. It caused a mild form of malaria in long-tailed monkey but caused lethal infections for rhesus monkey.

1932: using infected blood from macaques, it was demonstrated that these parasites could also infect human.

1965: the first documented human infection with *P. knowlesi.*

2004: a large focus of naturally acquired *P. knowlesi* infection in human beings.

2008: as the true fifth human malaria pathogen, capable of infecting humans with a remarkable epidemiological impacts.



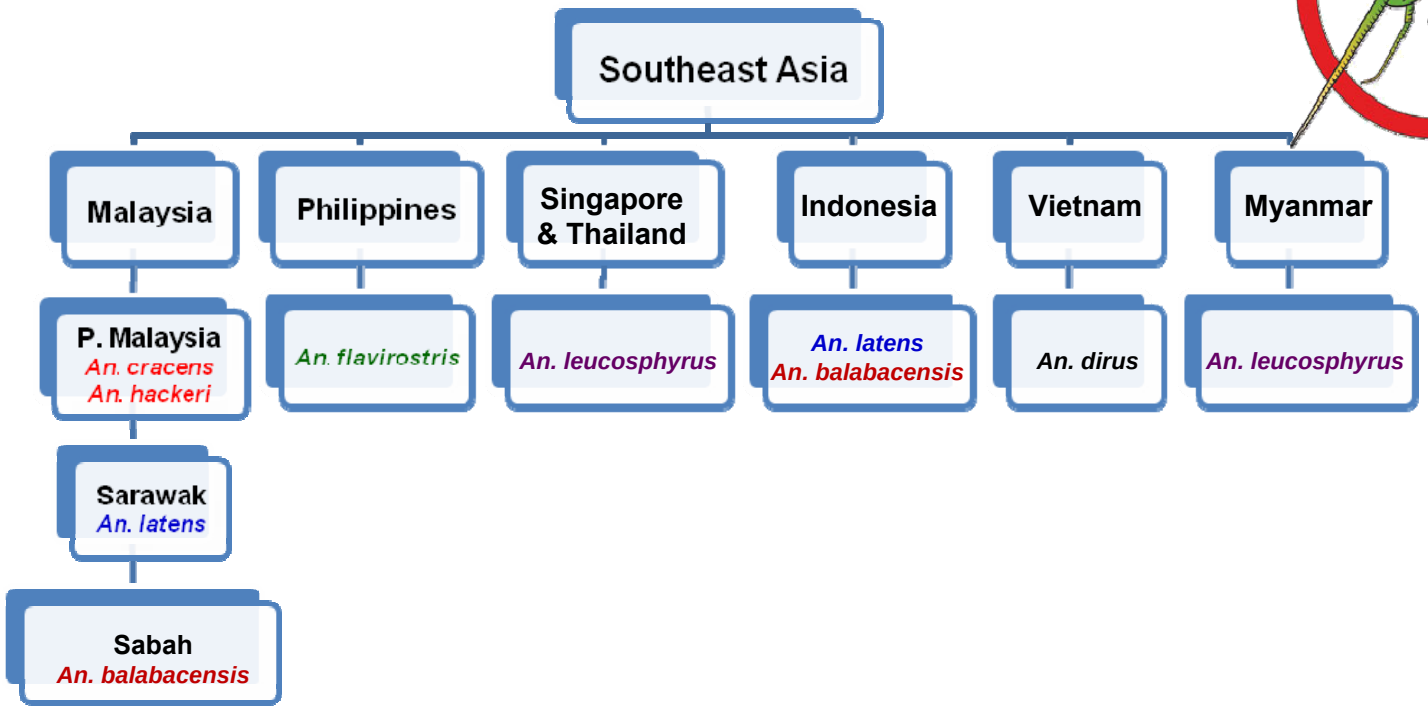
Knowles and Das Gupta, 1932; Chin et al, 1965; Singh et al, 2004; White, 2008

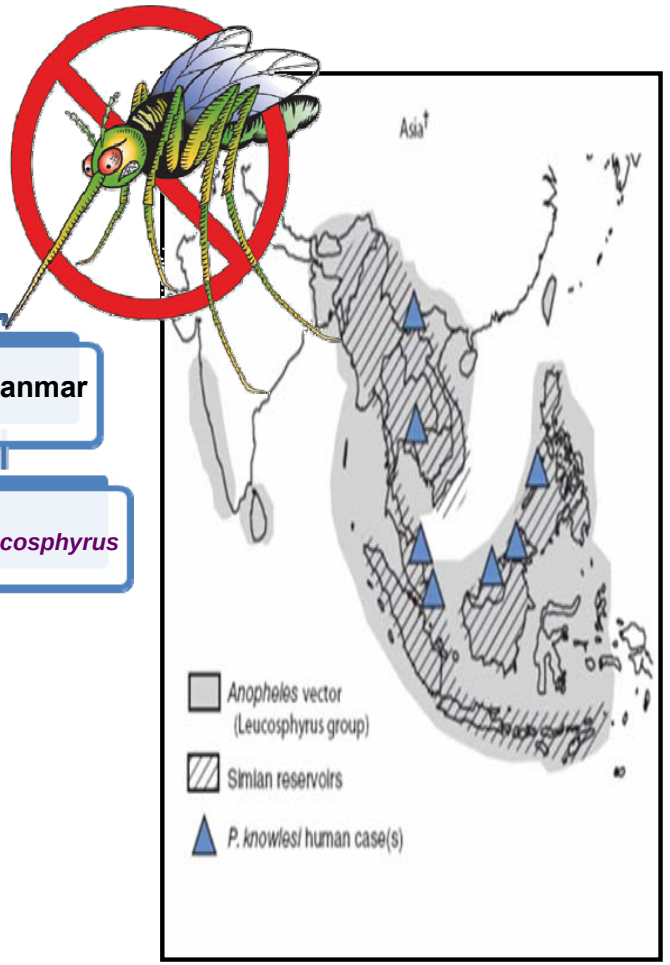
Malaria species of simian origin isolated in Asia and in South America

Simian *Plasmodium* species	Regional distribution	Human species resembling to them
Asia		
P. coatney	Malaysia, Philippines	*P. falciparum*
P. cynomolgi	India, Indonesia, Malaysia, Sri Lanka, Taiwan	*P. vivax*
P. eylesi	Malaysia	*P. vivax*
P. fieldi	Malaysia	*P. ovale*
P. fragile	India, Sri Lanka	*P. falciparum*
P. hylobati	Indonesia	*P. vivax*
P. inui	India, Indonesia, Malaysia, Philippines, Sri Lanka, Taiwan	*P. malariae*
P. Jeffrey	Indonesia, Malaysia	*P. vivax*
P. knowlesi	China, Indonesia, **Malaysia,** Philippines, Singapore, Thailand, Taiwan	***P. malariae, P. falciparum***
P. pitheci	Malaysia	*P. vivax*
P. simiovale	Sri Lanka	*P. ovale*
P. silvaticum	Malaysia	*P. vivax*
P. youngi	Malaysia	*P. vivax*
South America		
P. brasilianum	Brazil, Columbia, Mexico, Panama, Peru, Venezuela	*P. malariae*
P. simium	Brazil	*P. vivax*

CDC, 2009 and Sabbatani et al, 2010

Vectors of *P. knowlesi* in Southeast Asia





Wharton and Eyles, 1961; Jongwutiwes et al, 2004; Luchavez et al, 2008; Vythilingam, 2008; Tan, 2008; Jeslyn et al, 2010; Jiang et al, 2010 ; Sulistyaningsih et al, 2010; Vythilingam, 2010

Report on imported knowlesi malaria

Country	Year	Identifying method	H/O traveling	Occupation
USA American	1965	Blood passed into rhesus monkeys	Yes Malaysia	Employee in the US army
Finland Finnish	2007	Microscopy Nested PCR assay	Yes Malaysia	NA Traveler
Sweden Swedish	2006	Microscopy A rapid test PCR sequencing and phylogenetic analysis	Yes Malaysia	NA Traveler
USA American-Filipino	2008	Microscopy PCR sequencing	Yes Philippines	NA Visiting her home country
The Netherland Malaysian	2009	Microscopy PCR-sequencing	Yes Malaysian Borneo	A Rigger in the harbor of Rotterdam
Australia Australian	2010	Microscopy PCR-sequencing	Yes Kalimantan Indonesian Borneo	NA Traveler
Spain Spanish	2010	Microscopy RT-PCR-sequencing	Yes Indonesia, Malaysia, Thailand and Vietnam	NA Traveler

Coatney et al, 1971; Kantele et al, 2008; Bronner et al 2009; CDC, 2009; van Hellemond et al, 2009; Figtree et al, 2010

Knowlesi malaria…a regional concern?

Naturally acquired *P. knowlesi* malaria in human, Thailand

A 38-year-old Thai man, daily fever, headache, intermittent chill, sweating, and malaise for 4 days. He went to a hilly forest area in southern Thailand. He was frequently bitten by mosquitoes.

Medical history

Giemsa-stained showed the parasite structures was compatible with that of *P. malariae*.
DNA-based diagnostic method-Polymerase chain reaction (PCR) targeting SSU rRNA sequencing.

Diagnosis

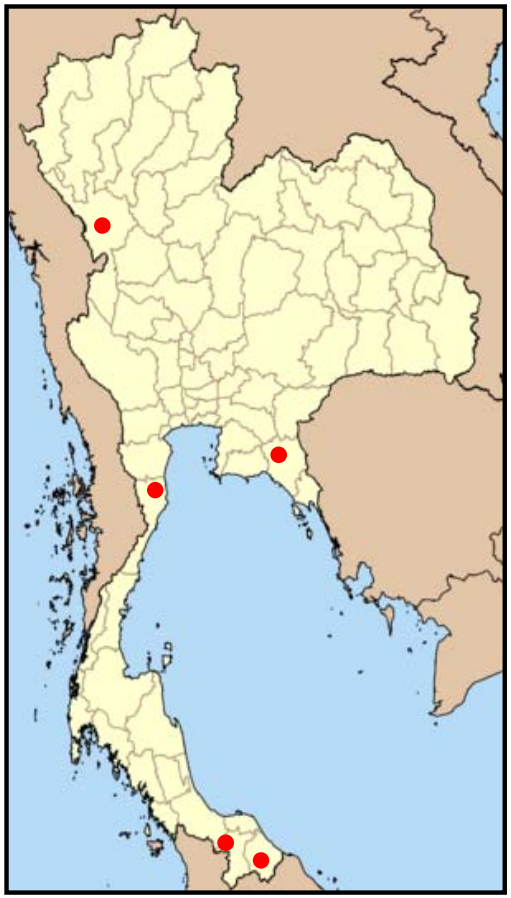
The patient was treated with 10 mg/kg of oral chloroquine initially, followed by 5 mg/kg, 6 hours later on day 1, and 5 mg/kg for the next 2 days.
PBS was negative for malaria within 2 weeks.

Treatment

Kongwutiwes et al, 2004

Demographic and parasitologic profiles in human knowlesi malaria

Patient data					Parasitologic data				
No	**Age**	**Sex**	**Ethnic**	**Location**	**Stage**	**Microscopy**	**PCR**	**Monkey**	**Season**
1	48	M	Thai	Prachuap Khiri Khan	Ring, schizont, gametocyte	*P. vivax*	Pv**, Pk**	Yes	Rainy
2	45	M	Thai	Prachuap Khiri Khan	Ring, trophozoite, gametocyte	*P. vivax*	Pv, **Pk**	Yes	Rainy
3	26	M	Thai	Narathiwat	Ring, trophozoite, gametocyte	*P. malariae*	**Pk**	Yes	Dry
4	39	M	Thai	Narathiwat	Ring, with double chromatin	*P. falciparum*	Pf, **Pk**	Yes	Rainy
5	35	F	Thai	Yala	Ring with double chromatin	*P. falciparum*	Pf, **Pk**	Yes	Rainy
6	17	F	Thai	Yala	Ring, trophozoite	*P. falciparum*	Pf, **Pk**	Yes	Dry
7	19	M	Thai	Yala	Ring, trophozoite	*P. vivax*	Pv, **Pk**	Yes	Rainy
8	46	M	Thai	Chantaburi	Ring, trophozoite, schizont	*P. falciparum*	Pf, **Pk**	No	Rainy
9	27	M	Myan mar	Tak	Trophozoite	*P. vivax*	Pv, **Pk**	No	Rainy
10	12	M	Myan mar	Tak	Ring with double chromatin, multiple infection	*P. falciparum*	Pf, **Pk**	No	Rainy



Putaporntip et al, 2009

Human natural infection of *P. knowlesi*, Myanmar

A blood film slide taken from a patient previously diagnosed as vivax malaria in Mojiang County, Yunnan province (Myanmar-China border area).

- **Patient's history**

Blood smear showed atypical forms, the ring forms had multinuclei, and the late trophozites trends to form band. The schizonts and gametocytes were somewhat alike *to Plasmodium vivax*.

PCR amplification was performed and confirmed that the patient was infected by *P. knowlesi*.

- **Diagnosis**

Zhu et al, 2006

Co-infections with *P. knowlesi* and other malaria parasites, Myanmar

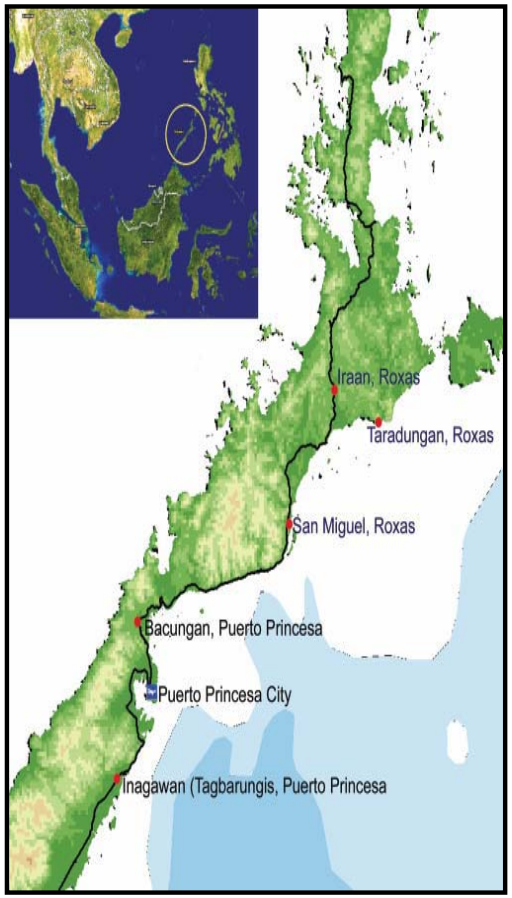
Plasmodium species identified in 146 persons in 2008	
Parasite	**No. (%) persons**
P. knowlesi	4 (2.7)
P. knowlesi/ P. falciparum	13 (8.9)
P. knowlesi/ P. vivax	13 (8.9)
P. knowlesi/ P. falciparum/ P. vivax	2 (1.4)
P. falciparum	51 (34.9)
P. vivax	53 (36.3)
P. falciparum/ P. vivax	10 (6.9)

Jiang et al, 2010

Human infections with *P. knowlesi*, the Philippines

Microscopy and PCR results of blood samples from Palawan, the Philippines

Patient	Age/Sex	Location	*Plasmodium* species	
			Microscopy	PCR
1	50/M	Bacungan, Puerto Princesa (PP)	Pf, Pm	**Pf, Pm, Pk**
2	49/M	Inagawan, Tagbarungis, PP	Pf, Pm	**Pk**
3	55/F	Caibulo, Iraan, Roxas	Pm	**Pk**
4	3/M	Balogo, San Miguel, Roxas	Pm	**Pk**
5	6/M	Maninguin, Iraan, Roxas	Pm	Pm
6	25/M	Minara, Roxas	Pm	Pm
7	10/F	Raradungan, Roxas	Pm	**Pk**
8	5/M	Bono-Bono, Bataraza	Pv, Pm	Pf, Pv, Pm
9	14/F	Bono-Bono, Bataraza	Pm	Pm
10	9/F	Inogbong, Bataraza	Pm	Pm
11	5/F	Inogbong, Bataraza	Pf, Pm	Pf, Pv



Luchavez et al, 2008

Naturally acquired human *P. knowlesi* infection, Singapore

Microscopically consistent with *P. malariae*. Nested PCR was performed and confirmed *P. knowlesi* after negative for other human *Plasmodium*.

Oral chloroquine was started for 3 days and blood smears were negative 3 days after treatment.

- **The first cases reported of a 20-year-old soldier in April, 2007. He had a fever of 4 days, myalgia, anorexia, nausea, vomiting. He had trained in the forest area inhabitated by the long-tailed macaque in North-western Singapore.**

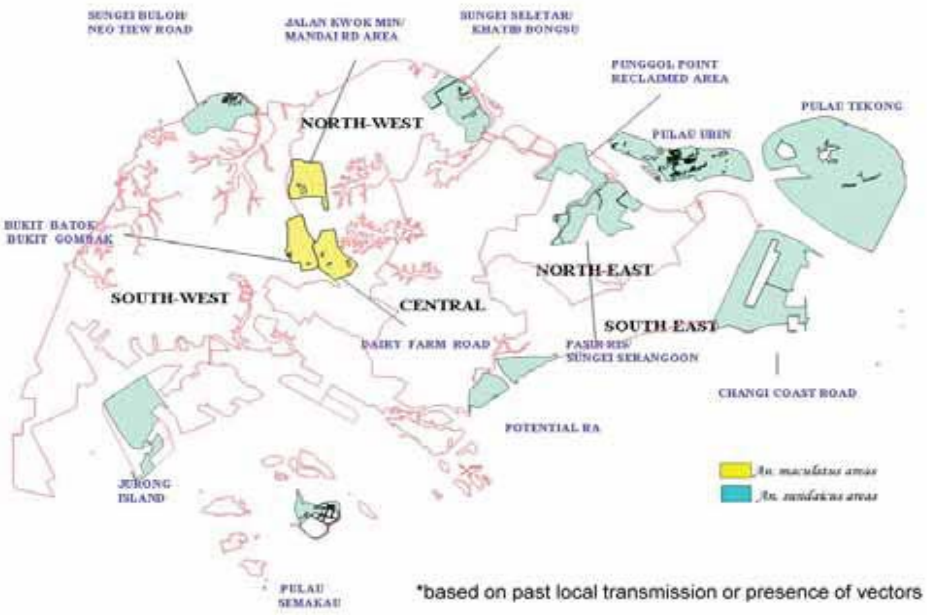
Microscopic blood examination showed mixed *P. falciparum* and *P. malariae* infections. Immunochromatographic rapid tests were positive for *P. falciparum* and mixed infections. Nested PCR was shown homology with *P. knowlesi*.

Oral chloroquine was given and he was well respond with no recurrent infection.

- **The second case was a 33-year-old Singaporean admitted in the hospital in October, 2007. He had a 3 days fever, malaise, nausea, and vomiting. He had just completed military reserve training in a forest area in North-western Singapore.**

Ng et al, 2008; Ong et al, 2009

Molecular epidemiological investigation of *P. knowlesi* in 6 human cases and macaques in Singapore



Keslyn et al, 2010

Human *P. knowlesi* infections in young children in central Vietnam

Background

Considering increasing reports on human infections by *P. knowlesi* in Southeast Asian countries, blood samples collected during two large cross-sectional malariometric surveys carried out in a forested area of central Vietnam in 2004 and 2005 were screened for this parasite.

Methods

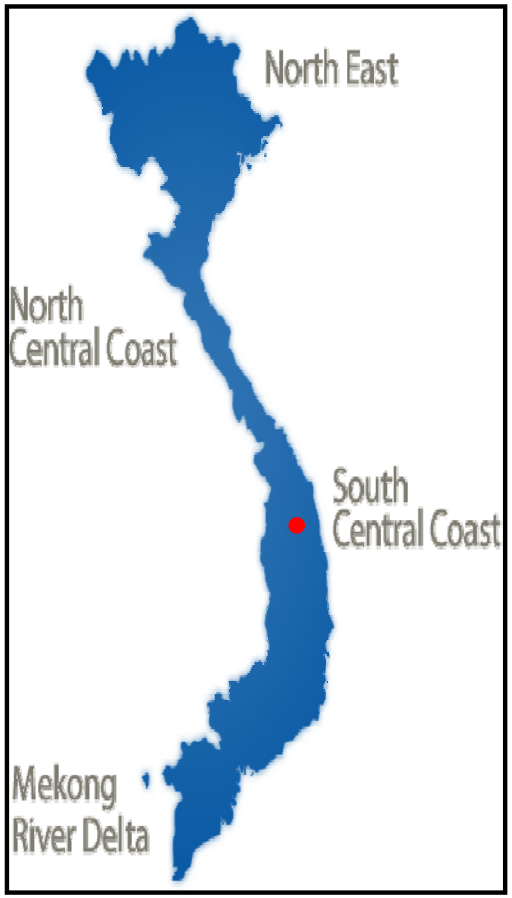
Ninety-five of blood samples with positive for *P. malariae* were randomly selected for performing PCR-sequencing analysis in detecting *P. knowlesi*. Family member of these positive cases were also screened.

Results

Five (5.2%) positive samples by PCR, three were confirmed to be *P. knowlesi* infections by sequencing, 2 young children of less than 5 years old and a young man.

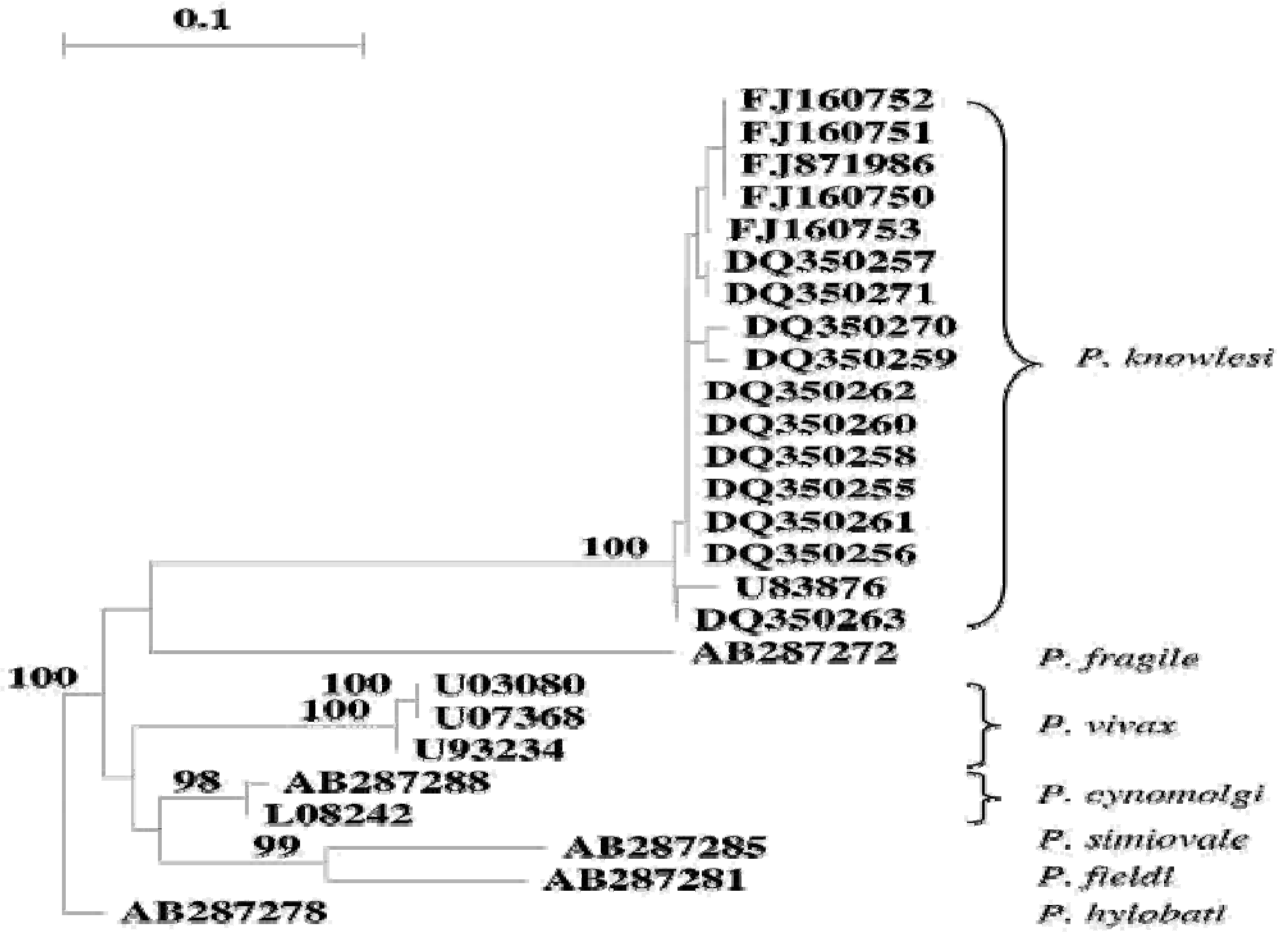
Conclusion

2/3 identified infections occurred in young children of < 5 years old. None of them was symptomatic either during the survey, or during passive case detection until one year after each survey.



Van den Eede et al, 2009; Cox-Singh, 2009; Nakazawa et al, 2009

P. knowlesi malaria in Vietnam: some clarifications



From the three human infections with *P. knowlesi* reported in the central Vietnam.

These findings contribute to the body of knowledge on the epidemiology of *P. knowlesi* malaria in Southeast Asia and cannot be easily dismissed as non-representative.

Large-scale studies to determine the extent and the epidemiology of *P. knowlesi* malaria in Vietnam are further needed.

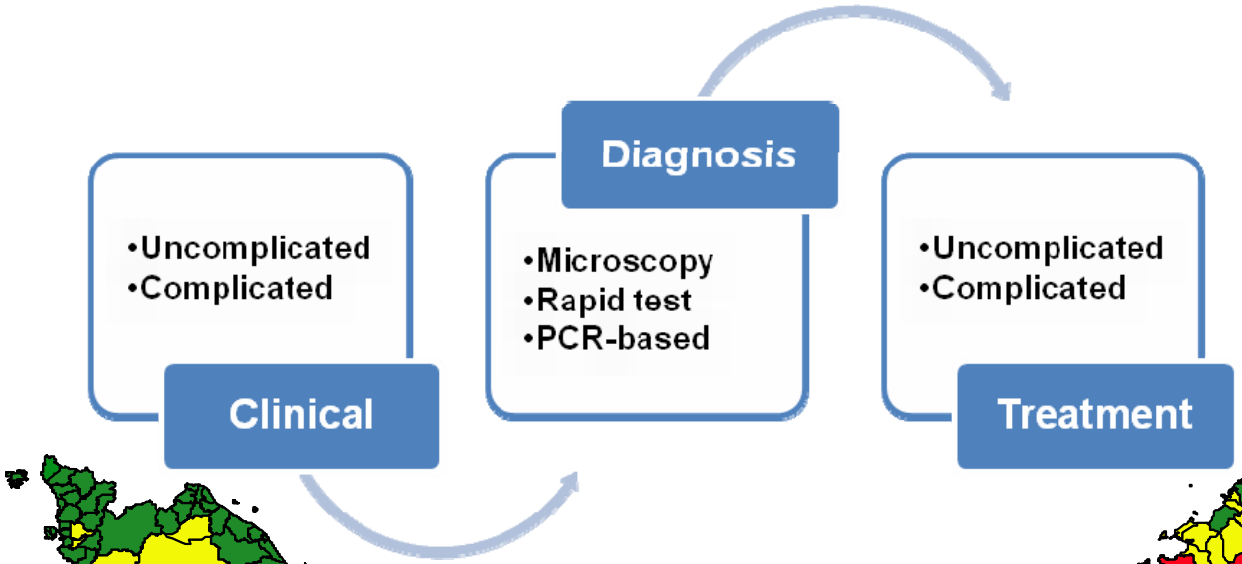
Van den Eede et al, 2010

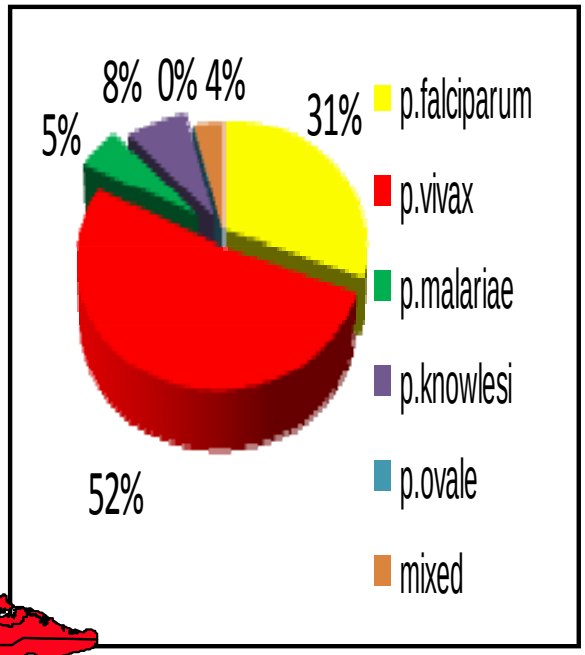
Profiles of *P. knowlesi*- positive patients, South Kalimantan province, Indonesia

Patient	Age, y	Microscopy-based diagnosis	PCR-based diagnosis	*P. knowlesi*-specific PCR for quality of 153-bp band	Sequence analysis
1	35	*Plasmodium falciparum*	*Plasmodium falciparum* *Plasmodium vivax* ***Plasmodium***	Strong	*Plasmodium vivax*
2	41	*Plasmodium falciparum*	*Plasmodium falciparum* *Plasmodium vivax* ***Plasmodium***	Strong	*Plasmodium vivax*
3	54	*Plasmodium falciparum*	*Plasmodium falciparum* *Plasmodium vivax* ***Plasmodium***	Weak	*Plasmodium vivax*
4	16	*Plasmodium falciparum*	*Plasmodium vivax* ***Plasmodium knowlesi***	Weak	*Plasmodium knowlesi*

Kulistyaningsih et al, 2010

P. knowlesi in Malaysia: from Monkey to Human and Genome





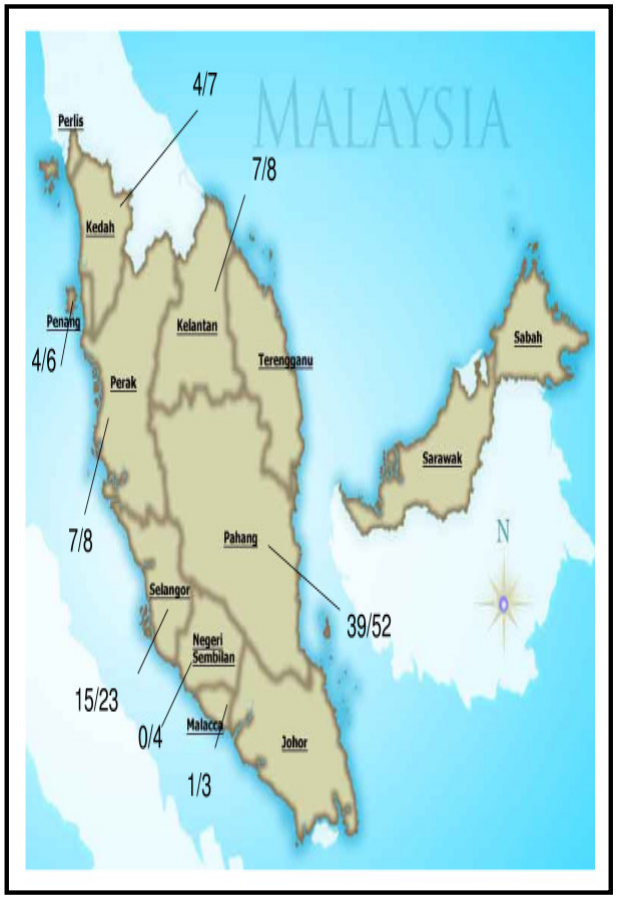
Malaria cases reported in 2008
***P. knowlesi* = 591/7390 (8%)**

Ministry of Health Malaysia, 2008

Knowlesi malaria in peninsular Malaysia

PCR results	Cases detected by microscopy					Cases detected by PCR
	Pf	Pv	Pm	Pf+Pm	Pm+Pv	
Pf	4	1	1	-	-	6
Pv	-	6	3	1	1	11
Pm	-	-	16	-	-	16
Pk	**2**	**1**	**62**	**-**	**-**	**65**
Pf+Pm	-	-	1	-	-	1
Pf+Pk	**-**	**-**	**2**	**-**	**-**	**2**
Pv+Pk		**1**	**5**	**-**	**1**	**7**
Pk+Pm	**-**	**-**	**3**	**-**	**-**	**3**
Total	**6**	**9**	**93**	**1**	**2**	**111**

***P. knowlesi* = 77 (69.4%)**



Vythilingam et al, 2008

Report on knowlesi malaria cases in Malaysian Borneo

Location	Year	Identifying method	No. of cases	Population	H/O traveling	Occupation
Pahang State Peninsular Malaysia	1965	Blood passed into rhesus monkeys	1	Adult 100%	Yes	Surveyor
Johor State Peninsular Malaysia	1971	Serology	1	Adult 100%	Yes	Field assistant
Sarawak State Malaysian Borneo	2004	Nested PCR assay	120	Adult 92.5%	85 Yes 35 NA	37 farmer, 28 logging camp workers, 5 housewives, 5 teachers, 18 others, and 27 NA
Sarawak State Malaysian Borneo	2008	Nested PCR assay	266	Adult 98.4%	NA	NA
Sabah State Malaysian Borneo	2008	Nested PCR assay	41	Adult 91.4%	NA	9 farmers, 3 logging camp workers, 2 housewives, 2 students, and 25 NA
Pahang State Peninsular Malaysia	2008	Nested PCR assay, sequencing of SSU rRNA and csp genes	5	Adult 80%	NA	NA

Chin et al, 1965; Fong et al, 1971; Singh et al 2004; Cox-Singh et al, 2008

Fatal cases of knowlesi malaria in Malaysian Borneo

Day	Case 1	Case 2	Case 3	Case 4
Day 1	A 66-year-old women presented to her local health post with a 3-day H/O epigastric pain, diarrhea, vomiting, fever and rigors. I/V and oral metronidazole was given.	A 69-year-old man, presented to a district hospital with a-7-day H/O fever and rigors, 3 days of diarrhea and severe abd. Pain, weakness, dysnea and cough. He had jaundice, and. Pain. **PBS: 75,000/µl for *P. malariae*.** Both I/V antibiotics and quinine were started.	A-39-yer-old man, was admitted to a district hospital with a 3-day H/O headache, fever and chills, vomiting, abd. Pain and syncope.	A 40-year-old man, with a 7-day H/O fever, chills and rigors, abd. Pain, headache and vomiting. Also, big spleen.
Day 2	Epigastric tenderness and I/V cimetidine was given. She remained anuric and poor response to I/V furosemide.		He was jaundice, hypotensive, abd. Pain and big spleen. **PBS: 112,000/µl for *P. malariae*.**	A severe malaria was suspected with a **thick blood film was shown P. malariae4^{+}.**
Day 3	She had jaundice and blood film of malaria was ordered. She still having abd. Pain and diarrhea. I/V antibiotics were given to cover sepsis. **Thick blood film showed 204,800/µl for *P. malariae*.** Chloroquine, sulfadoxine and pyrimethamine were given.	Hemolysis was started because of renal failure.	A diagnosis of severe malaria was made. Both I/V chloroquine, sulfadoxine and pyrimethamine were started but he remained anuric.	Oral chloroquine, sulfadoxine, pyrimethamine and primaquine were started.
Day 4	She died due to hypotensive and her conscious not improved.	She died the following morning.	He died of cardiovascular failure.	He developed ARDS with hemodialysis. He died on Day 13 with CVF.

Cox-Singh et al, 2008

A case report of fatal *P. knowlesi* infection with post-mortem findings

A formerly healthy 40 year-old male became symptomatic 10 days after spending time in the jungle of North Borneo. He had fever and body aches.

Four days later, he presented to hospital in a state of collapse and died within 2 hours.

He was hyponatraemic, and had elevated blood urea, potassium, thrombocytopenic and eosinophilic.

Blood for malaria parasites were indicated hyperparasitaemia[1] and single species *P. knowlesi* infection was confirmed by nested PCR.

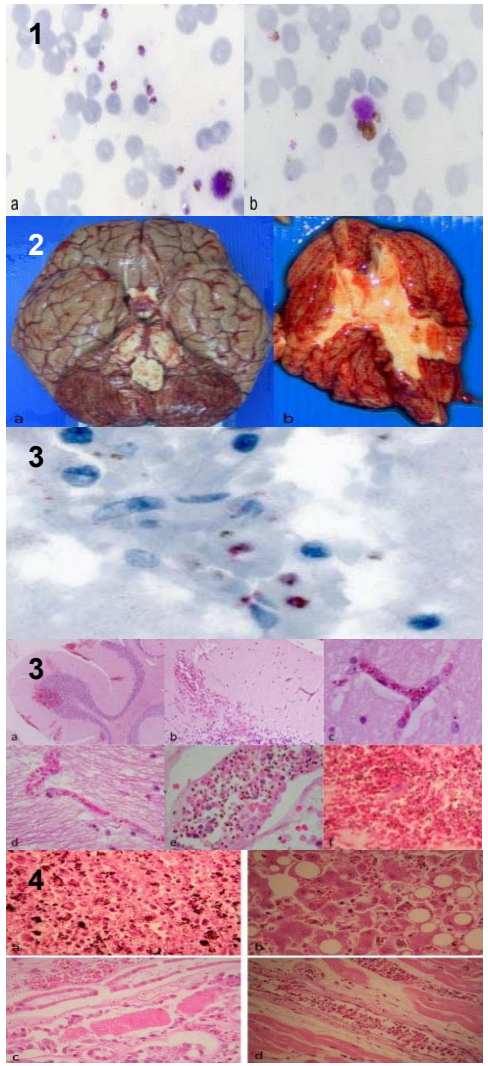
A pos-mortem was performed.

A blood sample showed >10% of erythrocytes infected with pigmented parasites.

Macroscopic pathology of the brain and endocardium showed multiple petechial haemorrhage[2], the liver and spleen were enlarged and with ARDS.

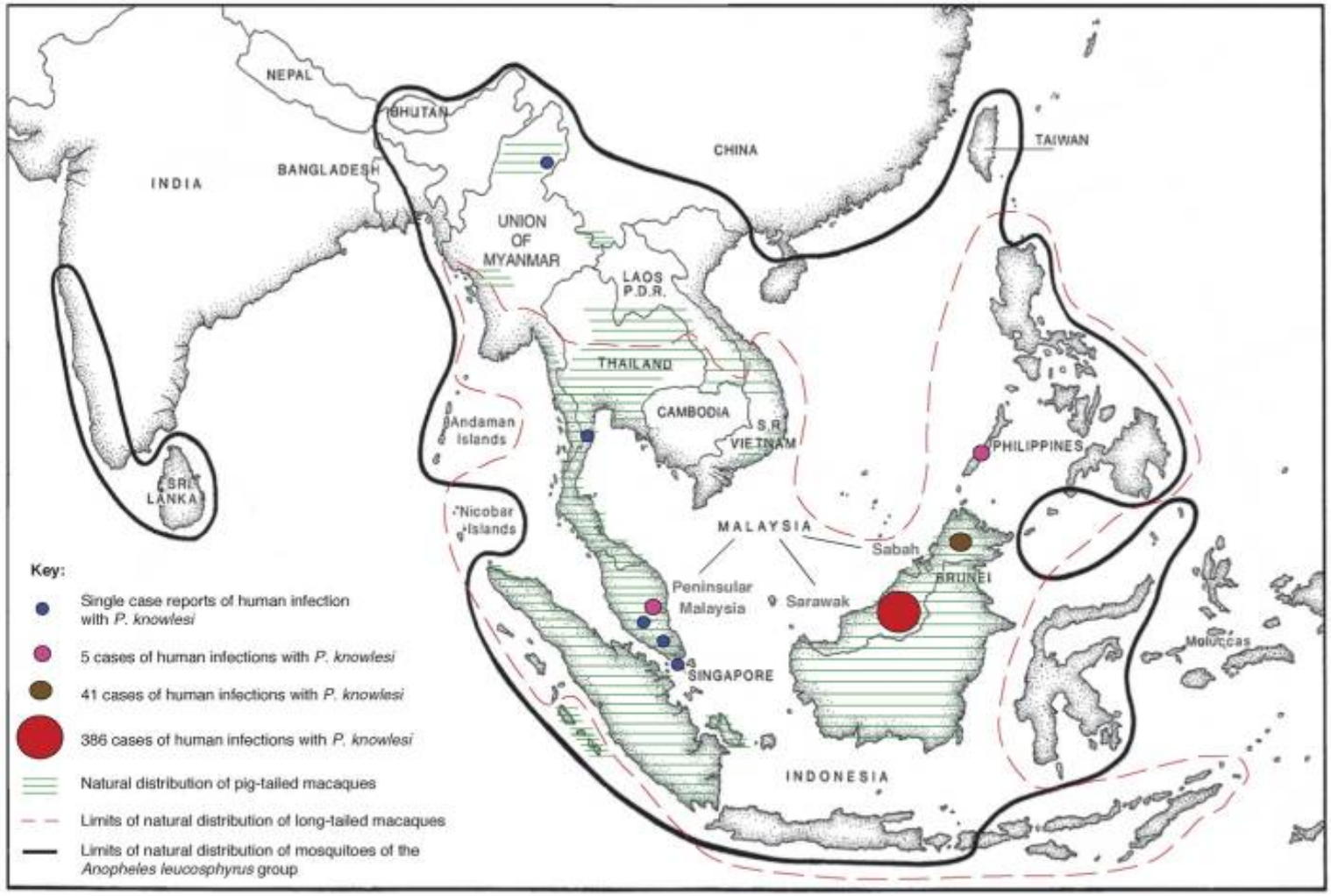
Microscopic pathology showed sequestration of pigmented parasitized RBC in the vessels of the brain[3].

The spleen and liver had abundant pigment containing macrophages and parasitized RBC[4].



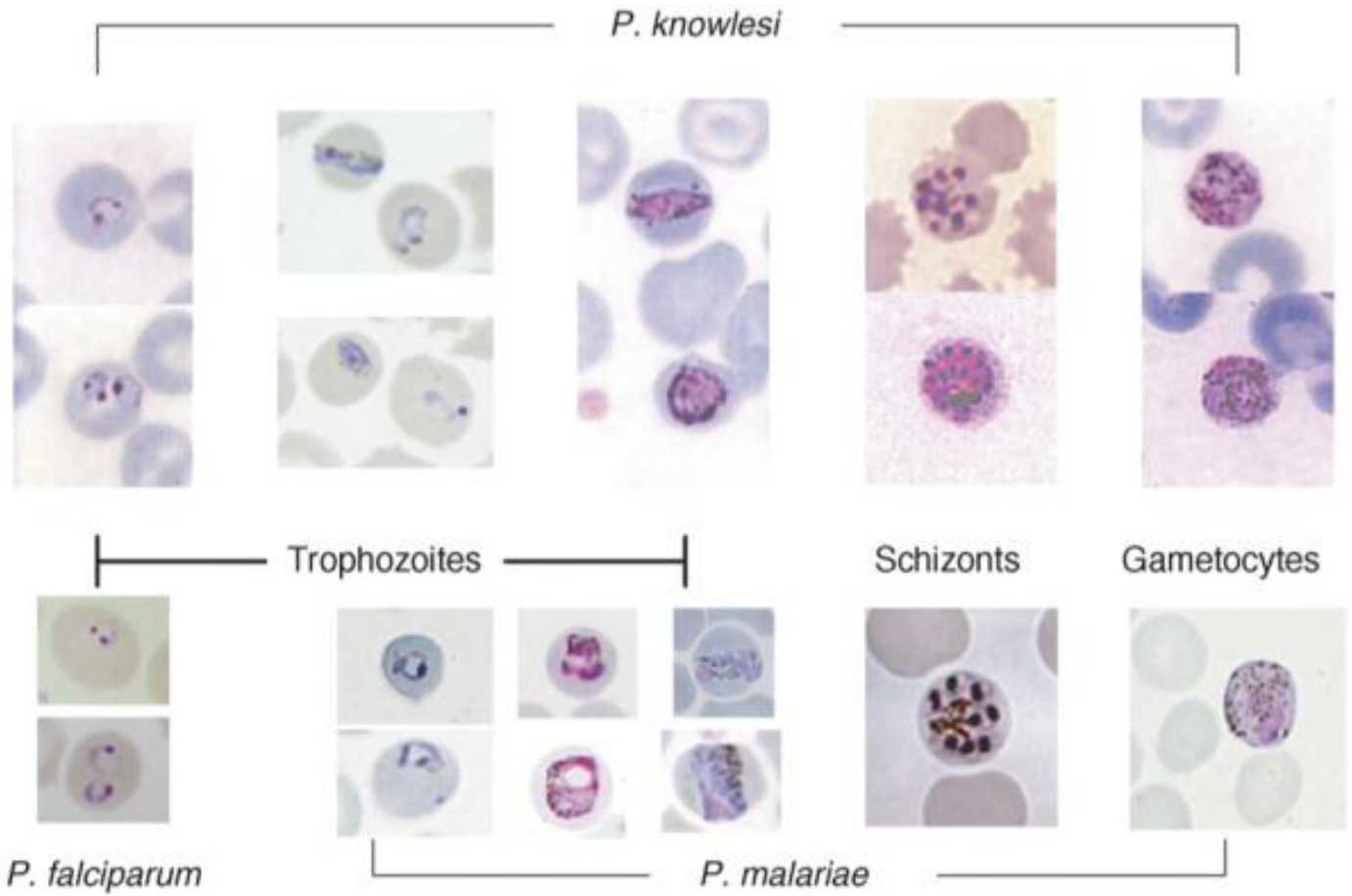
Cox-Singh et al, 2010

The distribution of reported human knowlesi malaria in Southeast Asia



Chin et al, 1965; Fong et al, 1971; Singh et al, 2004; Sallum et al, 2005; Fooden, 1982, 2006; Cox-Singh and Singh, 2008

Microscopy…a diagnostic dilemma?



The early trophozoites of both *P. falciparum* and *P. knowlesi* appear as discrete ring forms, at times with double chromatin dots, and individual erythrocytes can be infected by more than one parasite.

The late trophozoites, schizonts and gametocytes of *P. knowlesi* and *P. malariae* are both similar, including the appearance of some trophozoites as band forms.

Singh et al, 2004; Cox-Singh ad Singh, 2008

Rapid diagnostic tests…closer to reality?

Emerg Infect Dis. 2008 Nov;14(11):1750-2.

Use of malaria rapid diagnostic test to identify Plasmodium knowlesi infection.

McCutchan TF, Piper RC, Makler MT.

Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 12735 Twinbrook Pkwy, Rockville, MD 20892, USA. tmccutchan@niaid.nih.gov

Malar J. 2009 Jan 16;8:15.

Swedish traveller with Plasmodium knowlesi malaria after visiting Malaysian Borneo.

Bronner U, Divis PC, Färnert A, Singh B.

Faculty of Medicine & Health Sciences, Malaria Research Centre, University Malaysia Sarawak, Kuching, Sarawak, Malaysia. ulf.bronner@karolinska.se

Emerg Infect Dis. 2009 Sep;15(9):1478-80.

Human Plasmodium knowlesi infection detected by rapid diagnostic tests for malaria.

van Hellemond JJ, Rutten M, Koelewijn R, Zeeman AM, Verweij JJ, Wismans PJ, Kocken CH, van Genderen PJ.

Erasmus University Medical Center, Rotterdam, the Netherlands.

Parasitol Int. 2009 Sep;58(3):300-2. Epub 2009 Jun 13.

Cross-reactivity in rapid diagnostic tests between human malaria and zoonotic simian malaria parasite Plasmodium knowlesi infections.

Kawai S, Hirai M, Haruki K, Tanabe K, Chigusa Y.

Center for Tropical Medicine and Parasitology, Dokkyo Medical University, Tochigi, 321-0293, Japan. skawai@dokkyomed.ac.jp

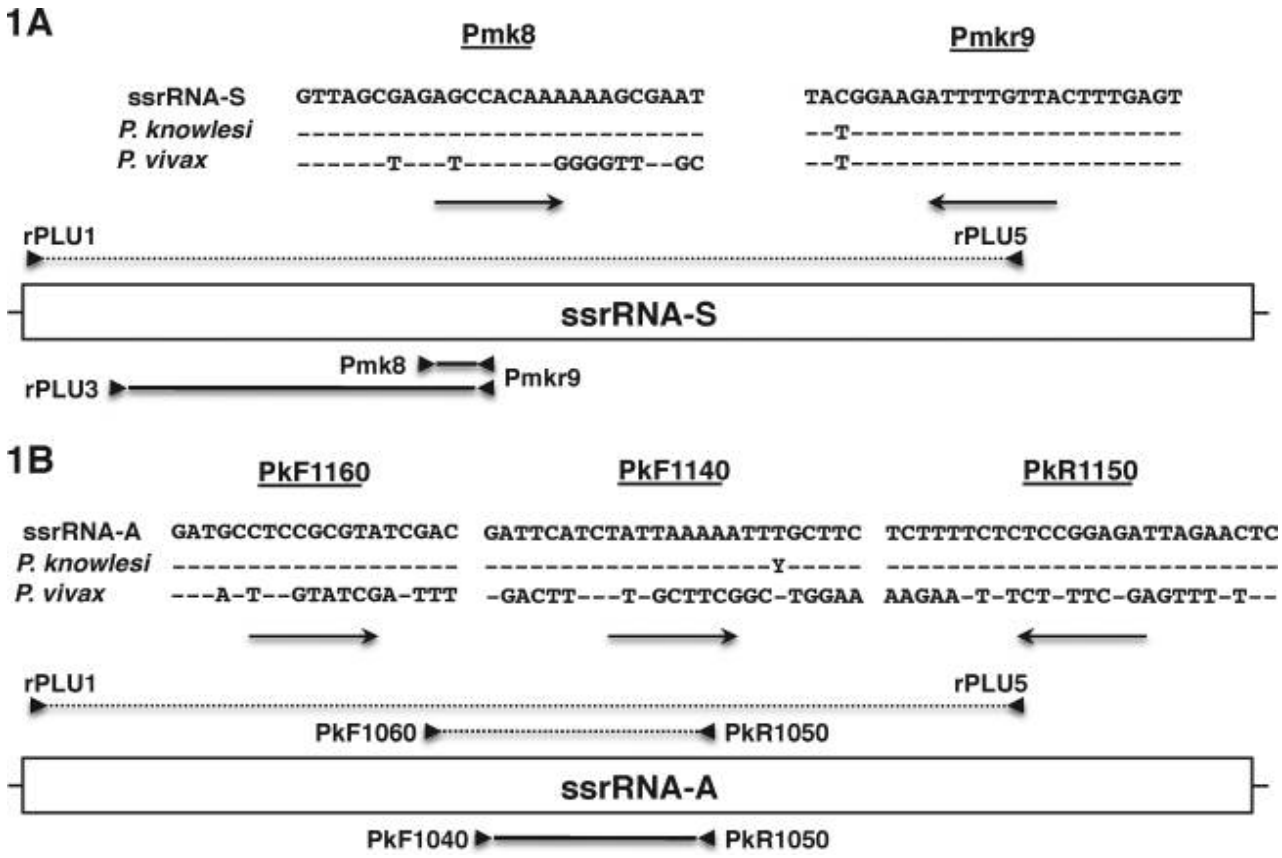
Binax NOW®
Binax INC., Maine, USA.
Designed to target the histidine-rich protein II (HRPII) antigen specific to all four human malaria species

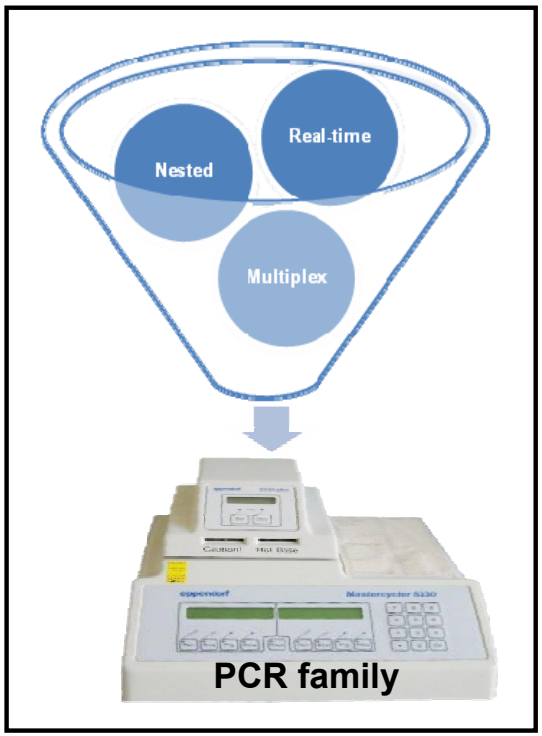
OptiMAL-IT
DiaMed AG, Cressier sur Morat, Switzerland.
Designed to detect pLDH of both *P. falciparum* and other plasmodia.

Entebe Malaria Cassette
Laboratorium Hepatika, Mataram, Indonesia.
Designed to detect PfHRP2 and *P. vivax* and specific for pLDH.

McCutchan et al, 2008; Bronner et al, 2009; Kawai et al, 2009; Ong et al, 2009; van Hellemond et al, 2009

PCR and knowlesi malaria…a confirm diagnosis ?





Lancet. 2004 Mar 27;363(9414):1017-24.

A large focus of naturally acquired Plasmodium knowlesi infections in human beings.

Singh B, Kim Sung L, Matusop A, Radhakrishnan A, Shamsul SS, Cox-Singh J, Thomas A, Conway DJ.

Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Kuching, Sarawak, Malaysia. bsingh@fmhs.unimas.my

Singh et al, 2004; Imwong et al, 2009; Van den Eede et al, 2009; Jiang et al, 2010; Sulistyaningsih et al, 2010

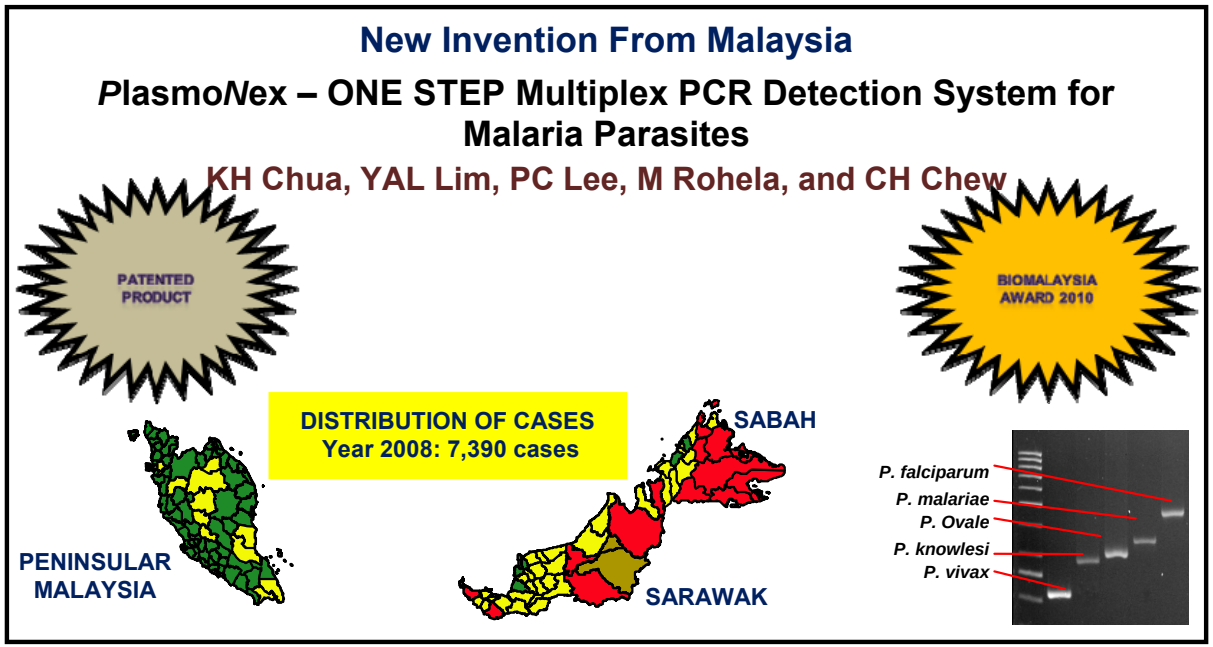
Multiplex-PCR…a promising tool in the future?

Emerg Infect Dis. 2010 Apr;16(4):672-4.

Plasmodium knowlesi in human, Indonesian Borneo.

Figtree M, Lee R, Bain L, Kennedy T, Mackertich S, Urban M, Cheng Q, Hudson BJ.

Department of Microbiology and Infectious Diseases, Royal North Shore Hospital, Pacific Hwy, St. Leonards, Sydney, New South Wales 2065, Australia.melfi_gtree@yahoo.com.au



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First case of detection of Plasmodium knowlesi in Spain by Real Time PCR in a traveller from Southeast Asia.

Ta TT, Salas A, Ali-Tammam M, Martínez Mdel C, Lanza M, Arroyo E, Rubio JM.

Malaria & Emerging Parasitic Diseases Laboratory, Parasitology Department, National Centre of Microbiology, Instituto de Salud Carlos III, Cra, Majadahonda Pozuelo Km, 2, Majadahonda, 28220 Madrid, Spain.

Figtree et al, 2010; Tang et al, 2010

LAMP…can be a gold standard?

J Clin Microbiol. 2010 Jul;48(7):2509-14. Epub 2010 May 5.

Evaluation of a loop-mediated isothermal amplification method as a tool for diagnosis of infection by the zoonotic simian malaria parasite Plasmodium knowlesi.

Iseki H, Kawai S, Takahashi N, Hirai M, Tanabe K, Yokoyama N, Igarashi I.

National Research Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido, Japan.

Transbound Emerg Dis. 2010 Apr;57(1-2):63-5.

Development of a loop-mediated isothermal amplification (LAMP) assay for rapid diagnosis of Babesia canis infections.

Müller H, Aysul N, Liu Z, Salih DA, Karagenc T, Beyer D, Kullmann B, Ahmed JS, Seitzer U.

Division of Veterinary Infection Biology and Immunology, Research Center Borstel, Borstel, Germany.

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Loop-mediated isothermal amplification method for differentiation and rapid detection of Taenia species.

Nkouawa A, Sako Y, Nakao M, Nakaya K, Ito A.

Department of Parasitology, Asahikawa Medical College, Midorigaoka Higashi 2-1-1-1, Asahikawa 078-8510, Hokkaido, Japan.

Exp Parasitol. 2009 Apr;121(4):342-5. Epub 2008 Dec 25.

Rapid identification of Acanthamoeba from contact lens case using loop-mediated isothermal amplification method.

Lek-Uthai U, Passara R, Roongruangchai K, Buddhirakkul P, Thammapalerd N.

Department of Parasitology, Faculty of Public Health, Mahidol University, 420/1 Rajavithi Road, Rajathewee District, Bangkok 10400, Thailand. phulu@mahidol.ac.th

J Clin Microbiol. 2010 Oct;48(10):3698-702. Epub 2010 Jul 21.

Specific, sensitive, and rapid diagnosis of active toxoplasmosis by a loop-mediated isothermal amplification method using blood samples from patients.

Lau YL, Meganathan P, Sonaimuthu P, Thiruvengadam G, Nissapatorn V, Chen Y.

Department of Parasitology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. lauyeeling@um.edu.my

Int J Parasitol. 2010 Mar 1;40(3):327-31. Epub 2009 Sep 6.

Sensitive and rapid detection of Schistosoma japonicum DNA by loop-mediated isothermal amplification (LAMP).

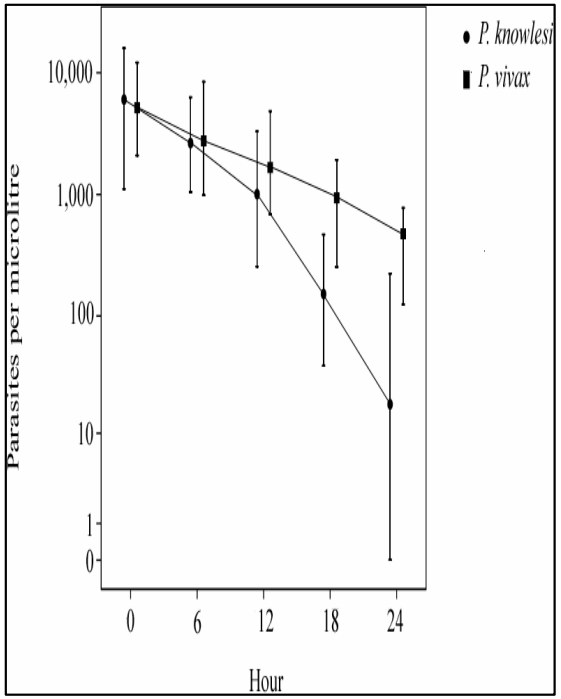
Xu J, Rong R, Zhang HQ, Shi CJ, Zhu XQ, Xia CM.

Medical College of Soochow University, Suzhou, Jiangsu Province, People's Republic of China.

PCR	LAMP
Merit	**Merit**
simple	simple
mass screening	mass sample survey
high sensitivity/specificity	High sensitivity/specificity
-	no need of equipments
Weak	**Weak**
equipments are needed	too high sensitivity
stable supply of reagents?	expensive reagents

Lek-Uthai et al, 2009; Nkouawa et al, 2009; Iseki et al, 2010; Iseki et al, 2010; Lau et al, 2010; Müller et al, 2010; Xu et al, 2010

Therapeutic approach



Parasite clearance during the first 24 hours of treatment with oral chloroquine. Graph shows median and 25%-75% interquartile ranges.

Uncomplicated knowlesi malaria

Anti-malarial regimens against *P. malariae*

Other non-*P. falciparum* malaria or uncomplicated *P. falciparum*

Complicated knowlesi malaria

Antimalarial regimens against severe *P. falciparum*

A novel drugs?

Demographic data (n=106)	
Age (years)	35·0 (15·9; 10–76)
Adults (>15 years)	97 (91·5%)
Men	71 (67%)
Clinical history and presentation (n=94)	
Temperature at admission (°C)	37·9 (1·1; 36–40·2)
Parasitaemia (parasites/μL blood)* at admission	2641 (80–117 600)
Duration of illness before admission (days)	4·5 (2·5; 1–14)
Fever, chills, and rigor	94 (100%)
Headache	30 (31·9%)
Cough	17 (18·1%)
Vomiting	15 (16·0%)
Nausea	6 (6·4%)
Diarrhoea	4 (4·3%)
Antimalarial treatment† and outcome (n=94)	
CQ (450 mg daily, days 1-3) + PQ (2–3 days or 2 weeks)	38 (40·4%)
CQ (600, 450 or 375 mg daily, days 1 and 2; 300 mg day 3)+PQ (3 days)	29 (30·9%)
CQ (600 mg day 1; 300 or 450 mg daily, days 2 and 3)+PQ (2–3 days)	14 (14·9%)
CQ (600 mg initial; 300 mg 6 h later and daily, days 2 and 3)+PQ (2–3 days or 2 weeks)	11 (11·7%)
Quinine (intravenous)	2 (2·1 %)
Days for parasite clearance from blood	2·4 (0·97; 1–3)
Days in hospital	3·3 (1·1; 1–7)

Data shown as n (% of total), or mean (SD; range) unless otherwise stated. CQ=chloroquine (dosage in mg base), PQ=primaquine (15 mg base for adults and 7·5 mg for children per day. *Data are geometric mean (range). †10 patients were also treated with one dose of 1000 mg sulfadoxine/50 mg pyrimethamine.

Demographic and clinical data for patients at Kapit hospital with single species *P. knowlesi* infection.

Singh et al, 2004; Daneshvar et al, 2010; Wilairatana et al, 2010

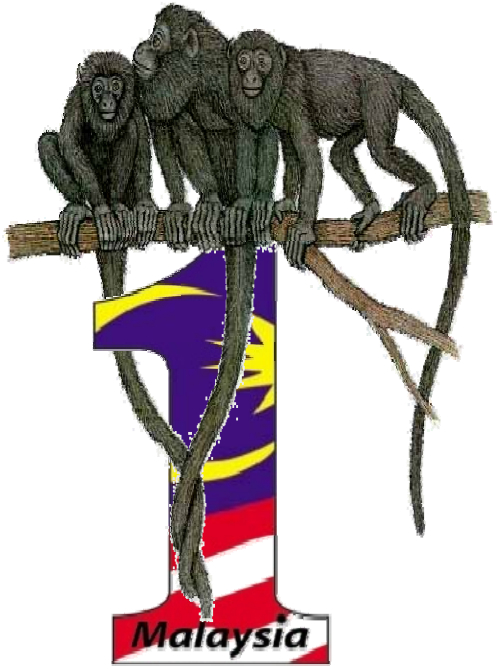
Conclusion…*P. knowlesi* as the fifth human malaria?

Epidemiology	• is recognized and confirmed of its potential virulence. • is the most widely distributed foci in Southeas t Asia.
Clinical perspective	• is based on location, clinical and microscopic findings. • the clinical diagnostic clue---CMA. PCR is the only accurate technique for making a definite diagnosis.
Future	• clinicians should be more aware due to it is easily misdiagnosed as a benign malaria and • infection with *P. knowlesi* in travelers to this region have been increasing.

PK

In Memory of
The late Prof. Dr Sornchai Looareesuwan

A living legacy



Thank you for your kind attention

Malaria Research Group

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