Plasmodium knowlesi current status and the request for review by an Evidence Review Group

Malaria Policy Advisory Committee
Geneva, Switzerland

Dr. Rabi Abeyasinghe
14 September 2016
Outline

• What is *Plasmodium knowlesi*
• WHO Consultation on *P. knowlesi* (2011)
• Brief history and current situation
• Transmission, hosts and vectors
• Diagnosis, clinical and treatment
• Estimating risk of infection
• Gaps in knowledge and next steps
What is *Plasmodium knowlesi*?

*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.
WHO Informal Consultation on the Public Health Importance of *P. knowlesi*

- Held in 2011 to review the *P. knowlesi* situation
- The Consultation provided 17 recommendations, many of which have contributed to our current understanding
- These included recommendations on diagnostics, determining vector and host distribution, protocols on diagnostic procedures and management among other areas
Brief history of *P. knowlesi*

*P. knowlesi* first isolated from a macaque imported into India from Singapore

The first naturally acquired human case reported in Peninsular Malaysia

A large focus of human cases was confirmed by molecular methods in Sarawak, Malaysian Borneo

1931

*P. knowlesi* proved capable of infecting humans in an experimental setting

1932

A second human case reported in Peninsular Malaysia

1965

1971

2004

Now

Human *P. knowlesi* cases confirmed in Member States throughout the region, primarily in Malaysia
First \textit{P. knowlesi} case reported in Peninsular Malaysia

No. published cases

1965

1\textsuperscript{st} naturally occurring transmission
A second case reported in Peninsular Malaysia

2nd naturally occurring transmission

1971

Malaria, Other Vectorborne and Parasitic Diseases (MVP)
WHO Western Pacific Regional Office (WPRO)
A larger focus of naturally acquired *P. knowlesi* infections was confirmed in blood samples from 2002-2004.

120 (58%) of 208 people with malaria tested positive for *P. knowlesi*.
Cumulative account of confirmed *P. knowlesi* cases in Peninsular Malaysia, Sabah and Sarawak, Malaysian Borneo

Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts

†Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts
Cumulative account of confirmed *P. knowlesi* cases in Peninsular Malaysia, Sabah and Sarawak, Malaysian Borneo

Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts

Peninsular Malaysia: 204

Malaysian Borneo: 3,122

†Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts
Current situation and distribution

Thailand: 37
Peninsular Malaysia: 204
Singapore: 6
Vietnam: 3
Philippines: 5
Yunan, China: 1
Myanmar: 33
Indonesia: 2
Malaysian Borneo: 3,122
Brunei (not shown): 1

2004-2015†

†Cumulative cases confirmed by PCR and/or sequencing and reported in peer-reviewed published manuscripts

Malaria, Other Vectorborne and Parasitic Diseases (MVP)
WHO Western Pacific Regional Office (WPRO)
Parasite species distribution in Malaysia, 2006-2015

- Pf
- Pv
- Pm
- Pk
- Po
- Mix

Source: Malaysia MoH
Proportion of parasite species from microscopy confirmed cases in Malaysia, 2011-2015

Data source: Malaysia MoH
Transmission and factors for zoonotic infections

HOST
Long-tailed macaque (M. fascicularis)
Pig-tailed macaque (M. nemestrina)
Banded leaf monkey (P. melalophus)

VECTOR
An. leucospyrus mosquitoes:
  - An. latens (Sarawak)
  - An. balabacensis (Sabah)
  - An. cracens (Peninsular Malaysia)
  - An. dirus (Viet Nam)

ENVIRONMENT
Dense jungle and forest fringe areas

MALARIA
Plasmodium knowlesi

SOCIAL
Employment
Migration
Others

Humans: Zoonotic infections

?
Natural hosts in Sarawak, Malaysian Borneo

Macaca fascicularis
Long-tailed macaque

Macaca nemestrina
Pig-tailed macaque

Natural hosts in Peninsular Malaysia and Myanmar

*Presbytis melalophus*
Banded leaf monkey
Peninsular Malaysia

*Macaca leonina*
Northern pig-tailed macaque
Myanmar

Source: koushik/naturism.co.in
Factors contributing to increase of reported *P. knowlesi* infections

- Improved diagnostic capacity
- Reduction in human malaria cases and awareness of Pk
- Loss of relative immunity due to low rates of malaria
- Change in land use patterns creating increased opportunity for spill over of infections to humans – through closer associations with natural reservoir hosts or access to infected vectors
Host-parasite interactions

- Two distinct *P. knowlesi* populations identified in human patients from Malaysia have been linked to *M. nemestrina* and *M. fascicularis*, respectively
  - The strain associated with *M. fascicularis* is thought to be circulating and infecting humans in areas of continental Asia, where *M. nemestrina* is absent
  - This *M. fascicularis*-associated strain may have a distinct relationship with environmental and socioeconomic variables compared to the mixture of parasite infections in patients from Malaysia
- The presence of Leucosphyrus Complex vectors in Malaysia including Dirus Complex vectors in continental Asia further adds to the possibility of different relationships between disease risk and the environment in these two regions
Vectors

• *P. knowlesi* vectors are members of the *An. leucosphyrus* group
  – found throughout the region
  – associated with dense jungle and forest fringe
  – rest and feed outdoors (exophagic) typically after dusk

• In Sarawak the forest breeding *An. latens* was found to be the primary vector
  – *An. latens* has been found to harbor other simian malaria parasites: *P. inui*, *P. coatneyi*, and *P. fieldi*

• *An. balabacensis* implicated as vector in Sabah and it prefers to breed in ground pools formed in fruit orchard, rubber and palm oil plantations

• *An. cracens* is considered a major knowlesi malaria vector in peninsular Malaysia

• *An. dirus* appears to be the primary vector in Viet Nam and continental Asia
An. lantens

Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016
An. balabacensis

Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016
An. cracens

Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016
Vector habitat

Slow running streams

Animal foot paths

Source: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, 2016
Vector habitat

Stagnant water

Ground pools

Sources: Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia, and EntoPest Unit of Sabah Health Department, Malaysia, 2016
Larval sampling

Source: EntoPest Unit of Sabah Health Department, Malaysia, 2016
Host and vector range

Diagnosis

- *P. malariae* and *P. knowlesi* may not be reliably distinguished by microscopy
  - PCR is the definitive diagnostic method
- pan-Plasmodium RDTs can be used for screening but not confirmation of *P. knowlesi*
- *P. knowlesi*-specific RDTs have demonstrated low sensitivity
  - Products are in the pipeline but performance to date is not yet optimal
Late trophozoite

Compared to *P. malariae*, bandform is imperfect and smaller in size. Coarse dark pigments are also present.

Source: Malaysia National Public Health Laboratory, MoH
Arrangement of merozoites are fairly malformed unlike P. malariae's rosette schizonts. Chromatin size is smaller compared to P. malariae.

Cytoplasm is also in fragments unlike the compact cytoplasms observed in P. malariae.

Source: Malaysia National Public Health Laboratory, MoH
Early Trophozoite
Gametocyte
Late trophozoite
Chromatin smaller compared to *P. malariae*
Late trophozoite
Presence of coarse dark pigments unlike brownish/yellow pigments observed in *P. malariae.*

Source: Malaysia National Public Health Laboratory, MoH
Clinical symptoms and parasitemia

• Most human *P. knowlesi* cases are chronic and symptomatic but some can be severe leading to death
  - Clinical studies in Sarawak, Malaysian Borneo, indicated > 10% of patients with *P. knowlesi* malaria developed severe disease as classified by the WHO with approximately 1% CFR

• *P. knowlesi* has the shortest asexual replication cycle of all Plasmodium species leading to rapidly increased parasitemia levels
  - High parasitemia is associated with severe *P. knowlesi* malaria
  - Patients having parasitemia >50,000 parasites/ul should be treated urgently and closely monitored until parasitemia is controlled
Treatment

• *P. knowlesi* is highly sensitive to artemisinins; and variably and moderately sensitive to chloroquine and mefloquine

• ACT KNOW open-label, random controlled trial (2016) compared artesunate-mefloquine (A-M) and chloroquine (CQ) for the treatment of uncomplicated *P. knowlesi* malaria
  – A-M treated patients showed improved outcomes, demonstrating:
    • faster parasite clearance than CQ treated patients
    • lower risk of anaemia within 28 days
    • faster fever clearance
    • shorter duration of hospital bed occupancy
Estimating risk of infection

- A recent exercise to map the risk of *P. knowlesi* infection in the GMS resulted in suggesting surveillance priorities

- There is a need to better understand the distribution of *P. knowlesi*

- Efforts are required to increase surveillance of parasite, vector, and host in areas of Thailand, Myanmar, Indonesia, Vietnam and Cambodia as well as across Malaysia

Map of estimated *P. knowlesi* malaria risk (Shearer, 2016)
Gaps in knowledge

- Determine if human-human transmission is occurring (experimental infections confirmed in the lab in 1960s, development of gametocytes in humans confirmed in 2009).
- Incidence of *P. knowlesi* infection in humans throughout its range and additional information on common clinical outcomes.
- Range and distribution of primary hosts and vectors including their bionomics.
- Sensitivity and suitability of available RDTs.
- Most effective methods of control and prevention of *Pk* infections.
- Likely impact on the success of malaria elimination campaigns.
Number of microscopy confirmed cases in Malaysia by parasite species, 2011-2015

Data source: World Malaria Reports, 2012-16 (draft)
*P. ovale, P. malariae & mixed (2011-12: mixed only)
Conclusions and next steps

• Modelling (Imai et al. 2014, Brock et al. 2016) suggest that human-vector-human transmission is plausible but is likely to be rare.

• There is a need to better understand the current and likely future changes that may influence this status and even levels of exposure to zoonotic *P. knowlesi*.

• Unique enabling technologies may be needed to limit *P. knowlesi* transmission to humans - appropriate mitigating and preventive strategies should be sought.

• A proposal for an ERG is requested to address gaps in knowledge and advise on a path towards elimination.
Acknowledgements;
Dr James Kelley, STC, MVP WPRO
Ms Jamie Kim, Intern MVP WPRO

Thank you.
References


References


Dr. Rohani Ahmad, Institute of Medical Research (IMR), Malaysia
EntoPest Unit of Sabah Health Department, Malaysia, 2016
References


