EXPERT CONSULTATION ON PLASMODIUM KNOWLESI MALARIA TO GUIDE MALARIA ELIMINATION STRATEGIES

1–2 March 2017
Kota Kinabalu, Malaysia
Expert Consultation on Plasmodium Knowlesi Malaria to Guide Malaria Elimination Strategies
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MEETING REPORT

EXPERT CONSULTATION ON \textit{Plasmodium knowlesi} MALARIA TO GUIDE MALARIA ELIMINATION STRATEGIES

Convened by:

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

Kota Kinabalu, Malaysia
1–2 March 2017

Not for sale

Printed and distributed by:

World Health Organization
Regional Office for the Western Pacific
Manila, Philippines
September 2017
NOTE

The views expressed in this report are those of the participants of the Expert Consultation on *Plasmodium knowlesi* Malaria to Guide Malaria Elimination Strategies and do not necessarily reflect the policies of the World Health Organization.

This report has been prepared by the World Health Organization Regional Office for the Western Pacific for governments of Member States in the Region and for those who participated in the Expert Consultation on *Plasmodium knowlesi* Malaria to Guide Malaria Elimination Strategies, which was held in Kota Kinabalu, Malaysia from 1 to 2 March 2017.
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Keywords:
Malaria – prevention & control / Plasmodium knowlesi / Regional health planning
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>artemisinin-based combination therapy</td>
</tr>
<tr>
<td>An.</td>
<td>Anopheles</td>
</tr>
<tr>
<td>A-L</td>
<td>artemether–lumefantrine</td>
</tr>
<tr>
<td>AS-MQ</td>
<td>artesunate–mefloquine</td>
</tr>
<tr>
<td>CQ</td>
<td>chloroquine</td>
</tr>
<tr>
<td>EQA</td>
<td>external quality assurance</td>
</tr>
<tr>
<td>GTS</td>
<td>Global Technical Strategy for Malaria 2016-2030</td>
</tr>
<tr>
<td>HRP2</td>
<td>histidine-rich protein II</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>MPAC</td>
<td>Malaria Policy Advisory Committee (WHO)</td>
</tr>
<tr>
<td>NAAT</td>
<td>nucleic acid amplification test</td>
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<tr>
<td>P.</td>
<td>Plasmodium</td>
</tr>
<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>UK NEQAS</td>
<td>United Kingdom National External Quality Assurance Scheme</td>
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</table>
An expert consultation was convened by the World Health Organization (WHO) on 1–2 March 2017 in Kota Kinabalu, Malaysia to determine the current epidemiological situation of *Plasmodium knowlesi* and recommend prevention and control strategies to accelerate malaria elimination. The objectives of the consultation were: to review available evidence and studies on *P. knowlesi*, particularly its transmission to determine its current epidemiological status; (2) to consider if there is human-to-human transmission of *P. knowlesi*; and (3) to discuss and recommend strategies for control and prevention of *P. knowlesi*, including vector control, diagnosis and treatment. The meeting was a follow-up of the WHO Informal Consultation on the Public Health Importance of *P. knowlesi*, held in Kuching, Sarawak, Malaysia in 2011.

*P. knowlesi* is a zoonotic malaria parasite, transmitted between non-human primate hosts by *Anopheles* mosquitoes and causing zoonotic infections in humans where the parasite, vector, primate host and humans converge. Long-tailed (*Macaca fascicularis*) and pig-tailed (*Macaca nemestrina*) macaques are the natural hosts of *P. knowlesi*.

Malaysia, which is targeting malaria elimination by 2020, still has the highest reported burden of *P. knowlesi* (69% of reported cases, mostly mono-infection) with 2327 cases in 2016, particularly in Sabah and Sarawak. However, cases are also reported in Cambodia, Indonesia, Myanmar, the Philippines, Thailand and Viet Nam. Three vectors have been reported to be capable of transmitting *P. knowlesi* in Malaysia: *Anopheles balabacensis* in Sabah, *An. latens* in Sarawak and *An. maculatus* in Peninsular Malaysia. These vectors are early biters, exophagic and exophilic, and thus are less affected by long-lasting insecticidal nets and indoor residual spraying. The majority of those affected by zoonotic malaria are forest workers, traditional planters and estate workers.

Early diagnosis of *P. knowlesi* infection is important as severe *P. knowlesi* malaria with cerebral manifestations are reported to develop at lower parasitaemic densities than with severe *P. falciparum* infections, and therefore necessitates early aggressive management. However, diagnosing *P. knowlesi* using rapid diagnostic tests (RDTs) and microscopy is currently not possible. Current confirmatory diagnosis is based on polymerase chain reaction (PCR). With microscopy, it is hard to distinguish *P. knowlesi* from *P. falciparum* in early blood stage parasites and *P. knowlesi* from *P. malariae* in later stages. This might lead to misdiagnosis especially in areas were *P. knowlesi*, *P. malariae* and *P. falciparum* are common. RDTs, on the other hand, are mainly developed for *P. falciparum* and *P. vivax*. These are not evaluated or tested against *P. knowlesi*. Nucleic acid amplification tests are more accurate than microscopy and RDTs but are not cheap and rapid, and may not be readily available in rural settings. PCR tests must be standardized for quality assurance purposes and comparison of results.

Clinical trials conducted on the treatment of uncomplicated *P. knowlesi* malaria showed that both chloroquine and artemisinin-based combination therapies (ACTs) (artemether–lumefantrine and artesunate–mefloquine) are highly effective against *P. knowlesi*, with ACTs providing faster parasite and fever clearance, thus earlier hospital discharge and lower bed capacity. For the treatment of severe *P. knowlesi*, retrospective studies showed that intravenous artesunate is effective. Prompt and accurate recognition of severe disease is vital.

Malaria has been on the notifiable disease list of Malaysia since 1988. In 2010, this list was updated to include *P. knowlesi* as a notifiable disease. Microscopically detected *P. falciparum*, *P. vivax* and *P. ovale* cases are subject to national quality assurance, while reported *P. malariae* and *P. knowlesi* samples are automatically sent to a laboratory for PCR confirmation of final diagnosis. If there is a discordant diagnosis for *P. falciparum*, *P. vivax* and *P. ovale* after quality assurance, this is also sent for PCR before the final diagnosis. Particularly in Sabah, where *P. knowlesi* cases are high, all cases are automatically sent to laboratories for PCR and quality-assured for final diagnosis. In Sarawak, the
directive is that all cases diagnosed as *P. malariae* by microscopy are reported as *P. knowlesi*, unless the patient has a history of travel overseas.

Currently, there is no evidence of widespread human–mosquito–human transmission, though limited transmission may be occurring in some situations. The meeting concluded that *P. knowlesi* infection remains primarily a zoonotic infection, but stressed the need to further investigate the possibility of human–mosquito–human transmission. Areas of research that would provide conclusive evidence to establish whether human-to-human transmission is occurring in nature were identified. Further research is needed on: parasite epidemiology, virulence and population genetics; development of point-of-care diagnostic tools; distribution and mapping of cases, vectors and macaques; and clinical management.

Countries are encouraged to engage in research studies to address knowledge gaps. They need to confirm *P. knowlesi* cases through PCR. In areas where there is no microscopy and PCR, RDTs with histidine-rich protein II (HRP2) may be used to exclude *P. falciparum*, but such positives need to be referred to a hospital laboratory where microscopy or PCR is present. Laboratories conducting PCR for *P. knowlesi* are encouraged to enrol in WHO’s external quality assessment scheme for nucleic acid amplification test. Countries should also standardize case definition and investigation for *P. knowlesi* and they are requested to report on *P. knowlesi* separately and not as Pm/Pk or non-*P. falciparum*.

WHO should determine relevance and implications of *P. knowlesi* infections to malaria elimination efforts in countries such as Malaysia. Global guidelines on *P. knowlesi* are largely based on data from Malaysia. Since there is new evidence of wider geographic spread and different clinical manifestations, WHO should consider these new data to support guideline revisions if necessary.
1. INTRODUCTION

*Plasmodium knowlesi* is a zoonotic malaria parasite, transmitted between non-human primate hosts by *Anopheles* mosquitoes and causing zoonotic infections in humans where the parasite, vector, primate host and humans converge. It was first isolated and studied in India in the early 1930s, and the first human cases of *P. knowlesi* malaria have been reported from many other countries in Southeast Asia. Knowlesi malaria is the leading cause of malaria in Malaysia, particularly in Sarawak and Sabah. Populations that are particularly at risk are people who live in or travel to forests and forest fringes where macaques and *P. knowlesi* vectors are commonly found.

There have been a number of studies in the last 5–10 years on epidemiology and clinical manifestations of *P. knowlesi*. However, there are still significant gaps in understanding knowlesi malaria and its current epidemiological status. Key knowledge gaps include: determining whether human–mosquito–human transmission is occurring, the epidemiological distribution of *P. knowlesi* infection in humans and common clinical outcomes, the range and distribution of *P. knowlesi* infection in the primary hosts and the vectors capable of transmitting the disease, their bionomics and control, the sensitivity of available malaria rapid diagnostic tests (RDTs), the most effective methods of control and prevention, and understanding the potential impact of continuing *P. knowlesi* transmission on the success of national malaria elimination programmes.

With three countries in the World Health Organization (WHO) Western Pacific Region aiming for malaria elimination by 2020, one of the main challenges for Malaysia, which is one of those three countries, remains the prevention and control of knowlesi malaria. Thus it is important to identify control and prevention strategies and to address key knowledge gaps that could impact negatively on these efforts. Recognizing this need, the WHO Malaria Policy Advisory Committee (MPAC), during its biannual meeting in September 2016 in Geneva, recommended the creation of an Evidence Review Group on *P. knowlesi* to provide evidence-based information and options for recommendations. The expert consultation was convened to bring together researchers, epidemiologists, clinicians, public health experts and representatives from the Ministry of Health of Malaysia to determine the current epidemiological situation of *P. knowlesi* and to recommend prevention and control strategies to accelerate malaria elimination.

The objectives of the consultation were:

1) to review available evidence and studies on *P. knowlesi*, particularly its transmission to determine its current epidemiological status;
2) to consider if there is a human-to-human transmission of *P. knowlesi*; and
3) to discuss and recommend strategies for control and prevention of *P. knowlesi*, including vector control, diagnosis and treatment.

2. PROCEEDINGS

The WHO Expert Consultation on Plasmodium knowlesi Malaria to Guide Malaria Elimination Strategies was held on 1–2 March 2017 in Kota Kinabalu, Malaysia. Dr Rose Nani Binti Mudin, Head of Vectorborne Disease Control, Ministry of Health of Malaysia, gave the welcome address, on behalf of Datuk Dr Lokman Hakim Bin Sulaiman, Deputy Director General of Health, Ministry of Health of Malaysia, the host country. Dr Rabindra Abeyasinghe, Coordinator, Malaria, other Vectorborne and Parasitic Diseases, WHO Regional Office for the Western Pacific, read the welcome address by Dr Shin Young-soo, WHO Regional Director for the Western Pacific.
Seventeen temporary advisers from Australia, Malaysia, Indonesia, Sri Lanka and the United Kingdom of Great Britain and Northern Ireland; six observers from the Ministry of Health of Malaysia; and three Secretariat staff from WHO attended the consultation.

The agenda of the meeting is provided in Annex 1 and the list of temporary advisers, observers and the Secretariat is provided in Annex 2.

2.1 Technical session 1: Epidemiological review of knowlesi malaria

2.1.1 Introduction to the Regional Action Framework for Malaria Control and Elimination in the Western Pacific (2016-2020) – Rabindra Abeyasinghe

The Regional Action Framework for Malaria Control and Elimination in the Western Pacific (2016-2020) is guided by the WHO Global Technical Strategy for Malaria 2016–2030 (GTS) and has three goals: (1) reduce mortality due to malaria in the Western Pacific Region by 50% and morbidity by at least 30%, by 2020, relative to 2015 baselines; (2) achieve malaria elimination in three countries by 2020; and (3) establish and maintain elimination-capable surveillance systems in all malaria-affected countries of the Region by 2020. As with the GTS, the Regional Action Framework includes three pillars: (1) achieve universal access to malaria prevention, diagnosis and treatment; (2) accelerate efforts towards elimination and attainment of malaria-free status; and (3) transform malaria surveillance into a key intervention. The Framework also identifies a list of priority activities at the country level, among which is addressing the challenges posed by P. knowlesi.

2.1.2 Epidemiology of P. knowlesi in Malaysia: detection, surveillance, its host and vectors, and spatio-temporal distribution and trends – Rose Nani Binti Mudin

Malaria cases reported in Malaysia have been decreasing from 12,708 in 2001 to 2,327 in 2016. Indigenous malaria cases also decreased from 8,808 in 2001 to 304 in 2016. Starting 2008, the proportion and number of P. knowlesi cases increased as malaria laboratories established PCR facilities and P. knowlesi was made notifiable. Reported P. knowlesi cases in Malaysia increased from 376 cases in 2008 to 1,604 cases in 2016. Among the 1,604 cases reported in 2016, 8 cases were imported from Indonesia (5), Papua New Guinea (2) and Thailand (1).

In 2016, P. knowlesi cases contributed 69% of total reported cases. Disaggregated data from 2016 show that P. knowlesi affects more men than women (about 80%) with more cases in the adult age group (highest in adults over 55 years). Zoonotic malaria cases are more sporadic (i.e. individual cases) rather than clustered.

The spatial distribution of human malaria cases in Peninsular Malaysia in 2016 shows indigenous cases occur more in Kelantan and Perak while imported cases occur more in Selangor. In Sabah, indigenous cases occur mainly in rural areas (interior part of Sabah), while in Sarawak most cases are imported. For zoonotic malaria, the spatial distribution in Peninsular Malaysia in 2016 shows cases occurring mostly in border areas of Selangor; while in Sarawak and Sabah cases are mostly in the interior parts (see Fig. 1).
The spatial distribution of vector species for zoonotic malaria in Malaysia shows different vectors in different states. In Peninsular Malaysia, *Anopheles cracens* are found in the north-east and Anopheles introlatus are found in the south-west. In Sabah, *Anopheles balabacensis* are found, while in Sarawak Anopheles latens are present (see Fig. 2).

The majority of those affected by zoonotic malaria are forest workers, traditional planters and estate workers (e.g. construction workers in the interior area who are building schools). Most zoonotic malaria occurs in traditional villages (60%), estate/farms (20%) and logging site (13%); and affects the Bumiputera Sarawak (43%) and Bumiputera Sabah (33%) ethnic groups.

2.1.3 *P. knowlesi* malaria in other countries – Kevin Baird

In 2008, *P. knowlesi* cases were reported in Sabah, Sarawak and Peninsular Malaysia and in Palawan, Philippines. In later years, *P. knowlesi* malaria cases were also reported in Cambodia, Indonesia,
Myanmar, Thailand and Viet Nam, but sampling has been limited and the full geographical extent of disease risk across most of the region, including within these countries, is unknown.

In 2016, Shearer et al. (2016) produced the first map of *P. knowlesi* malaria risk, based on land use, human population and presence of vectors, to identify priority areas for surveillance (see Fig. 3). The predicted map shows areas of high risk of *P. knowlesi* infection in Malaysia, Cambodia, Thailand, Viet Nam, Myanmar, the Lao People’s Democratic Republic, Indonesia and the Philippines.

**Fig. 3:** Predicted risk of *P. knowlesi* malaria ranging from low to high risk

![Map of predicted risk of *P. knowlesi* malaria ranging from low to high risk](image)


A 2017 survey in North Sumatra, Indonesia shows that 614 of 3731 participants (16.5%) were positive for malaria parasites by microscopy (Lubis et al., 2017). PCR detected parasite DNA in samples from 1169 individuals (31.3%). In total, 377 participants (11.8%) harboured *P. knowlesi*. Several studies were also cited indicating presence of *P. knowlesi* in Central Kalimantan, Indonesia (Setiadi et al., 2016) and in Khan Phu, Viet Nam (Maeno et al., 2017). Emerging evidence suggests asymptomatic *P. knowlesi* is as prevalent in humans as asymptomatic *P. vivax* and *P. falciparum* in some parts of Sumatra and perhaps Viet Nam.

### 2.1.4 Parasites, what do we know? – Balbir Singh

Several studies were cited to understand the *P. knowlesi* parasite. Lee et al. (2011) mentions that evolutionary analyses of sequence data indicate that *P. knowlesi* existed in monkeys prior to human settlement in Southeast Asia and underwent a recent population expansion. Further, it was considered that the current increase in the human population, coupled with ecological changes due to deforestation, could result in a switch to humans as the preferred host for this pathogenic *Plasmodium* species. Divis et al. (2015) showed that malaria parasite *P. knowlesi* in humans is an admixture of two highly divergent parasite populations, each associated with different forest-dwelling macaque reservoir host species; and that although both *P. knowlesi* types co-exist in the same areas, the
divergence between them is similar to or greater than that seen between subspecies in other sexually reproducing eukaryotes.

Assefa et al. (2015) indicated that in a genome sequencing analysis, zoonotic malaria parasite *P. knowlesi* consists of three highly divergent subpopulations. Two are commonly seen in sympatric human clinical infections in Malaysian Borneo (commonly seen in long-tailed and pig-tailed macaques) and a third type detected in a few laboratory-maintained isolates originally derived in the 1960s elsewhere in Southeast Asia.

2.1.5 Vectors of *Plasmodium knowlesi*: Bionomics – Indra Vythilingam

There are three vectors of *P. knowlesi* in Malaysia: *An. balabacensis* in Sabah, *An. latens* in Sarawak and *An. maculatus* in Peninsular Malaysia.


Recent studies found *An. latens* in Kapit (Vythilingam et al., 2006; Tan et al., 2008), *An. cracens* in Kuala Lipis (Vythilingam et al., 2008; Jiram et al., 2012), *An. introilatus* in H. Selangor (Vythilingam et al., 2014) and *An. balabacensis* in Kudat (Wong et al., 2015).

A summary of longitudinal studies indicate that *An latens* and *An cracens* are found more commonly in forest and farms than in villages; while *An. balabacensis* are found in all areas, i.e. farms, forests and villages (Vythilingam et al., 2016; Wong et al., 2015). Fig. 4 shows the biting times of *An. latens, An. cracens* and *An. balabacensis.*

**Fig. 4:** Biting times of three predominant vectors

[Graph showing biting times]

Sporozoite rate, parous rate and vectorial capacity of the three predominant vectors were discussed, in addition to the results of the nested PCR, which indicated the presence of several simian parasites in the vectors.

2.1.6 Patients – who are affected? – Nicholas Anstey

Age and gender distribution among affected patients in Sabah, Malaysia shows that from 2007 to 2014, patients with *P. knowlesi* are older than those with *P. falciparum* and *P. vivax* (median is 32, 23
and 24 years, respectively); 80% are male (in children, 65% are male); females with *P. knowlesi* are on the average older than males – that is, 38 versus 31 years old (45 versus 34 years old in adult populations); and a bimodal age distribution among females with peaks at 12 and 52 years (William et al., 2013; Rajahram et al., 2016). There are also several hospital-based studies of PCR-confirmed *P. knowlesi* where it shows that adults (at least 15 years old) and males are more affected.

Pregnant women appear to be at lower risk of acquiring *P. knowlesi*, in comparison to the risk of acquiring either *P. falciparum* or *P. vivax* infections. A study by Barber et al. (2015) shows that in two referral hospitals from 2010 to 2014, there were no pregnant women admitted with *P. knowlesi*, while there were 17 with *P. falciparum* and 7 with *P. vivax*.

There were also several studies cited that showed that farmers and those working in forest areas are more affected by *P. knowlesi*, including two cases from Cambodia where both cases were forest hunters. Studies also showed that parasitaemia and disease severity increase with age. From the Sabah Ministry of Health notifications from 2010 to 2014, there is 0% mortality in 373 children. Severe *P. knowlesi* is not yet reported in children less than 12 years old and the youngest reported death from *P. knowlesi* is 31 years (age range is 31–84 years). In 2016, Malaysia reported 8 deaths (case fatality rate 0.09) following *P. knowlesi* infections.

### 2.1.7 Non-human primate reservoirs of *Plasmodium knowlesi* – Reuben Sunil Kumar Sharma

The natural hosts of *P. knowlesi* that were initially identified were long-tailed (*Macaca fascicularis*) and pig-tailed (*Macaca nemestrina*) macaques. The long-tailed macaque is the most abundant and widespread non-human primate in Southeast Asia. It is common to see them in urban areas in most cities, as well as in recreational parks, and suburban and agricultural areas. It has a broad habitat range from coastal mangroves to inland hill forests (home range: ca 1.2 square kilometres; daily movement: ca 1900 square metres). It has the highest occurrence of human–animal conflict in Malaysia and is considered an invasive wildlife species in many countries. *Macaca fascicularis* has at least 10 recognized subspecies and is semi-terrestrial, diurnal and omnivorous. It can live up to 30 years in captivity.

There is currently no comprehensive survey on macaques and existing studies are not comparable; that is, techniques used were different. However, several studies were summarized that show the prevalence of *P. knowlesi* infection among long-tailed macaques in Southeast Asia. This is shown in Table 1.

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
<th>Prevalence (%)</th>
<th>Year</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>East Malaysia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarawak</td>
<td>82</td>
<td>86.6</td>
<td>2011</td>
<td>Lee et al.</td>
</tr>
<tr>
<td>Sabah</td>
<td>26</td>
<td>15.4</td>
<td>2014</td>
<td>Zhang et al.</td>
</tr>
<tr>
<td>West Malaysia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pahang</td>
<td>75</td>
<td>13.3</td>
<td>2008</td>
<td>Vythilingam et al.</td>
</tr>
<tr>
<td>Selangor</td>
<td>70</td>
<td>30.0</td>
<td>2015</td>
<td>Akter et al.</td>
</tr>
<tr>
<td>West coast</td>
<td>781</td>
<td>13.6</td>
<td>2017</td>
<td>Sharma et al.</td>
</tr>
<tr>
<td>Indonesia</td>
<td>31</td>
<td>32</td>
<td>2007</td>
<td>Jones-Engel et al.</td>
</tr>
<tr>
<td>Thailand – southern</td>
<td>99</td>
<td>61</td>
<td>2008</td>
<td>Seethamchhai et al.</td>
</tr>
<tr>
<td>Thailand – southern</td>
<td>195</td>
<td>5.6</td>
<td>2010</td>
<td>Putapornpit et al.</td>
</tr>
<tr>
<td>Singapore</td>
<td>13</td>
<td>23.1</td>
<td>2011</td>
<td>Jeslyn et al.</td>
</tr>
<tr>
<td>Lao People's Democratic Republic</td>
<td>44</td>
<td>2.3</td>
<td>2012</td>
<td>Zhang et al.</td>
</tr>
</tbody>
</table>
2.2 Technical session 2: Diagnosis and clinical management

2.2.1 Laboratory diagnostics for *P. knowlesi* – Balbir Singh

Microscopy is still the most widely used method for detection of malaria in rural settings since it is a relatively cheap, rapid, quantitative and sensitive technique. However, it is hard to morphologically distinguish *P. knowlesi* from *P. falciparum* in early stages (early ring forms) and *P. knowlesi* from *P. malariae* in later stages (blood stages). This could result in misdiagnosis, especially in areas where *P. knowlesi* transmission co-exists with *P. malariae* and/or *P. falciparum*.

There are minor morphological differences between *P. knowlesi* and *P. malariae*. In *P. knowlesi*, a mature schizont can have up to 16 merozoites, while in *P. malariae*, schizonts can have up to 6–12 merozoites. However, mature schizonts are not seen in every *P. knowlesi* infection. In *P. knowlesi*, the late trophozoite has sometimes an amoeboid cytoplasm, while in *P. malariae*, late trophozoites have a compact cytoplasm. However, these minor differences can be missed in busy routine laboratories where only thick blood films are normally examined as microscopists have limited time to screen a large number of samples and also when parasitaemia is low.

Before PCR assays were used in 2004, confirmation of *P. knowlesi* was by injection of blood into rhesus macaques where parasites will increase and eventually kill the monkey.

Currently available malaria rapid diagnostic tests (RDTs) have been mainly developed for detection of *P. falciparum* and *P. vivax* infections. These are not evaluated or tested against *P. knowlesi* as the number of *P. knowlesi* cases is small in comparison with the two other species. One of the first diagnostic tests that could detect *P. knowlesi* is a monoclonal for *P. falciparum* that cross-reacts with *P. knowlesi* (OptiMAL-IT). If this test is used and is positive for *P. falciparum*, then it could be either *P. falciparum* or *P. knowlesi*. There are three studies that evaluated the sensitivity of RDTs against *P. knowlesi* (Barber et al., 2013; Foster et al., 2014; Grigg et al., 2014). OptiMAL-IT has the highest sensitivity at 72% for *P. knowlesi* (45% sensitive for < 1000 parasites per microlitre [µL]). Basically, currently available RDTs are not useful for identifying *P. knowlesi* infections.

Using a nucleic acid amplification test (NAAT) is more accurate in detecting *P. knowlesi*. The sensitivity of different assays was summarized. Nested PCR can detect 1–6 parasites/µL of blood; single-step PCR can detect 1 parasite/µL; real-time PCR can detect 10–100 copies/µL and loop-mediated isothermal amplification (LAMP) can detect 10–100 plasmid copies/sample. Factors that can affect PCR amplification/sensitivity include template and volume used (whole blood or blood spots), extraction method for DNA template (crude or highly purified), type/brand of DNA polymerase used (including volume), and type of thermocycler used (different sampling times). Nested/real-time PCR are more sensitive and specific than microscopy but this is not used in routine diagnostic laboratories in rural hospitals or clinics in Southeast Asia. PCR can be used for confirmation/validation.

In Sarawak, 2475 malaria cases were PCR-confirmed and 1276 were *P. knowlesi*. There were 12 *P. malariae* cases, all imported. The directive in Sarawak is that all cases diagnosed as *P. malariae* by microscopy are reported as *P. knowlesi*, unless the patient has a history of travel overseas.

2.2.2 Development of field-based/point-of-care diagnostic tools for *Plasmodium knowlesi* – Lau Yee Ling

The ideal characteristics for a point-of-care test in resource-limited settings are: affordable (US$ 0.18 per test), sensitive (few false negatives), specific (few false positives), user-friendly (minimal training requirements), rapid (enable immediate treatment) and robust (no cold chain), equipment-free, and delivered to those who need it.
RDTs are so far the most promising point-of-care diagnostic tool. It is user-friendly (can be performed by workers with minimal training), rapid (can be done in 15–20 minutes) and cost-effective (about US$ 0.32 per test), and can detect parasitaemia of > 100 parasites/µL. However, there is no commercially available RDT for *P. knowlesi*.

Several field tests of RDTs were performed for the detection of *P. knowlesi*. BinaxNOW Malaria can detect *P. knowlesi* by detecting *Plasmodium* aldolase (pALD) with a sensitivity of 23% and will increase to 45% if parasitaemia is increased (> 10 000 parasites/µL). OptiMAL RDT (DiaMed) can detect *P. knowlesi* by detecting lactate dehydrogenase (PfLDH) with a sensitivity of 25% in samples with parasite counts < 1000/µL and 97% with parasite counts > 1000/µL. Other RDTs tested were Paramax-3 and Entebbe Malaria Cassette which can detect *P. knowlesi* as *P. vivax*. There were also studies on potential antigenic candidates, but so far results are not promising.

Limitations in using RDTs include: HRP2 deletion (thus needs improvement), inadequate quality control for RDT, and limited heat stability as field conditions exceed manufacturer storage recommendations.

Different point-of-care molecular tools for malaria diagnosis were also presented. The Accutas system is a lab-on-chip system for malaria diagnosis and can detect five species of *Plasmodium*; detection limit is 2 parasites/µL of blood; high sensitivity at 97.4% and specificity of 93.8% versus real-time PCR. Accutas can be performed directly with unprocessed blood (2 µL) and processing time is two hours. Another point-of-care molecular tool is TrueLab Uno, which uses an assay based on TaqMan chemistry. Its detection limit is < 5 parasites/µL for both *P. falciparum* and *P. vivax*; sensitivity and specificity is 100%. The Loopamp malaria kit (developed by Eiken Chemical Co.) uses simple preparation method of 35 µL of blood placed on a tube in the hot-block or water bath at 75°C for five minutes followed by LAMP. LAMP results are available within 60–90 minutes. Other point-of-care molecular tools are Illumigene Malaria LAMP workflow, nucleic acid lateral flow immunoassay-DIAGMAL70 and nanomal. All these point-of-care molecular methods were not tested specifically for *P. knowlesi* except Loopamp.

Molecular methods are the most efficacious in diagnosing *P. knowlesi* infections, but these tests can produce a false positive in *P. vivax* infections, require expensive equipment and are costly. An ideal diagnostic test for *P. knowlesi* infections that is potent, cost-effective and practically feasible in the resource-limited setting is yet to be developed.

### 2.2.3 Clinical management and treatment of *P. knowlesi* malaria – Timothy William

Microscopic misreporting of *P. knowlesi* as *P. malariae* has been associated with fatalities due to lack of severe disease recognition and delayed parenteral artesunate (Rajahram et al., 2012). *P. knowlesi*, like other malaria species, has non-specific symptoms and can present itself atypically, which may lead to fatal cases. Most patients have uncomplicated disease and so far no severe cases have been reported in children. The research definition of severe knowlesi malaria is a modification from *P. falciparum*, which includes respiratory distress, shock, jaundice, severe anaemia, significant abnormal bleeding, hypoglycaemia, metabolic acidosis, acute kidney injury and hyperparasitaemia. Previously, WHO and Malaysian Ministry of Health guidelines recommended chloroquine for *P. knowlesi*, which is the same for *P. malariae* where *P. knowlesi* infections are often misidentified as *P. malariae*. However, in the 2015 WHO Guidelines for the Treatment of Malaria, it was recommended that, “In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria with either ACT or chloroquine”. There were studies conducted on the treatment of uncomplicated *P. knowlesi* malaria.

One such study was on artemether–lumefantrine (A-L) versus chloroquine (CQ) where it also showed no treatment failure in either study arm by day 42 and no difference in adverse events or serious adverse events between groups (Grigg et al., 2017). However, A-L has better early therapeutic response and risk of anaemia at day 28 is lower (66%) compared to CQ at 81%. Another study
compared artesunate–mefloquine (AS-MQ) versus CQ in three district hospitals in Sabah, Malaysia (Grigg et al., 2016a) where it showed no treatment failures with either drug at day 42, which means both drugs are efficacious. However, AS-MQ shows better early therapeutic response and could also offer an alternative unified treatment policy for artemisinin-based combination therapy (ACT) for all *Plasmodium* species in co-endemic areas.

The current malaria treatment guideline of the Ministry of Health of Malaysia for *P. knowlesi* is A-L as first-line treatment and AS-MQ or CQ as second-line or alternative treatments. ACT is also recommended for uncomplicated *P. falciparum* and *P. vivax*. Malaysia, in effect, has a unified ACT guideline in co-endemic *P. knowlesi* areas. ACT also has faster parasite and fever clearance, earlier hospital discharge, and lower bed occupancy compared to CQ for *P. knowlesi* (for example, Malaysia has a policy of mandatory hospital admission). The ACT guideline also reduces the risk of CQ inadvertently being used for unrecognized severe knowlesi malaria. Primaquine (PQ) is not needed for *P. knowlesi* as it does not have hypnozoites and gametocytes can be cleared using ACT by day 7. For the treatment of severe knowlesi malaria, the 2015 WHO guideline for the treatment of severe malaria due to any *Plasmodium* species is intravenous (IV) or intramuscular artesunate for at least 24 hours or until they can tolerate oral medication, then complete treatment with 3 days of ACT. Retrospective studies show IV artesunate is effective for *P. knowlesi*.

Prompt and accurate recognition of severe disease is vital. Thus, in situations where health workers are unable to assess all clinical/laboratory severity criteria immediately, age and parasitaemia can be the best predictor of severe disease (Grigg et al., 2017). In areas where *P. knowlesi* is common, for severe *P. knowlesi* patients, it is recommended to have IV artesunate if parasitaemia is 15 000/µL. Some evidence on the onset of severe symptoms in *P. knowlesi* infections at lower parasite densities (10 000/µL) was discussed and it was suggested that newer evidence with a larger sample size should be studied before revising the definition of severe malaria.

Treatment of *P. knowlesi* in children is the same as in adults. For pregnant women, a study shows that CQ, quinine and AL all successfully cleared the parasites with a parasite clearance time of 1–3 days. The study concluded that although *P. knowlesi* is the commonest malaria species among females in Sabah, *P. knowlesi* is relatively rare during pregnancy. It may, however, be associated with adverse maternal and pregnancy outcomes (Barber et al., 2015; William et al., 2011).

Other supportive therapies for *P. knowlesi* and other parasite species were also discussed, including fluid management, renal replacement therapy and empirical antibiotics.

### 2.3 Technical session 3: Evidence review of human-to-human transmission of *P. knowlesi*

#### 2.3.1 Introduction of new international EQA scheme for NAAT methods – *Peter Chiodini (via Skype)*

In March 2014, WHO’s Malaria Policy Advisory Committee (MPAC) recommended the development of an international external quality assurance (EQA) system to ensure that data obtained from nucleic acid amplification assays are reliable and comparable. Thus, a meeting in June 2015 was conducted to: define customer requirements for the NAAT EQA scheme; identify the EQA materials and panels needed for an NAAT scheme; define the structure of the NAAT EQA scheme; identify strategies for resource mobilization; and reach consensus on the next steps, roles and responsibilities. The United Kingdom National External Quality Assurance Scheme (UK NEQAS) from the London School of Hygiene and Tropical Medicine was chosen as the collaborator for running the EQA scheme with sponsorship by the Foundation for Innovative New Diagnostics (FIND).

Specimen preparation, internal quality checks and specimens dispatched to laboratories were discussed. A total of 55 laboratories from 34 countries are currently registered with 10 specimens dispatched to each laboratory twice a year. This is composed of 500 µL of freeze-dried blood plus 50 µL of blood in dried blood spots format for both positive (all malaria species) and negative blood
samples. All samples were examined pre- and post-distribution by nested PCR and real-time PCR. Participating laboratories were asked to report on presence or absence of malaria parasite, species identification and parasitaemia. Laboratories were also asked for the methodology they used (e.g. RT-PCR, nested-PCR, primers, etc.). Initial results from the 28 laboratories that have submitted their results so far were presented. Based on these initial results, it was shown that lyophilized blood and dried blood spots proved to be effective and stable matrices as it was straightforward to reconstitute and extract the DNA and no cold-chain was involved. Initial results also highlighted the problems in reporting false positives and false negatives when assay specimens contained low parasitaemia or specimens contained non-P. falciparum species (especially P. knowlesi).

2.3.2 Is human-to-human transmission of Plasmodium knowlesi possible? – Indra Vythilingam

The P. knowlesi transmission cycle was presented and discussed. The distribution of forests, farms and villages; the movement of macaques and humans between these three areas; and the hypothesized transmission cycle of P. knowlesi in Malaysia and Southeast Asia were also presented. An interesting observation was noted in several studies. In Kapit and Kuala Lipis where there were a considerable number of monkeys in the study sites, only 12 mosquitoes (An. latens) and 4 mosquitoes (An. cracens) were found positive for the parasite, respectively. However, in Kudat, where monkeys were hardly seen, 96 An. balabacensis were found positive with the parasite. In other studies, An. balabacensis found in farms, forests and villages were dissected and showed multiple infections.

One major challenge in conducting studies to determine the presence of human-to-human transmission is that human landing catch is the only method that can be used to collect Anopheles. There are other methods that can be used, but very few Anopheles are collected. Other challenges are that the resting sites of mosquitoes are unknown or no data are currently available, and that catching monkeys to obtain specimens is not easy. To prove that human-to-human transmission is possible, researchers may need to feed mosquitoes infected human blood through a membrane feeder and determine if sporozoites can develop.

2.3.3 Molecular epidemiology and spatial distribution of Plasmodium knowlesi infecting macaques in Peninsular Malaysia – Reuben Sharma

Different Plasmodium species and their zoonotic potential were presented. P. knowlesi and P. cynomolgi were confirmed to cause human infections; while other species have high, moderate and low risk of zoonosis.

A study was presented where 781 long-tailed macaques were screened from 77 locations (urban, suburban, agricultural, and secondary forests) on the west coast of Peninsular Malaysia using nested PCR – 185 SSU rRNA (279 bp). Results revealed that 13.6% of the macaques were positive for P. knowlesi infection; 26.4% were positive for P. inui; 17.7% were positive with P. cynomolgi; 12.8% for P. coatneyi; and 11.8% for P. fieldi. Hotspots for P. knowlesi infection in Macaca fascicularis on the west coast for Peninsular Malaysia were shown as well as the prevalence of P. knowlesi in Macaca fascicularis in different habitats. The study concluded that there is a high prevalence of P. knowlesi infection among long-tailed macaques in Peninsular Malaysia. The infection is no longer restricted to forest-dwelling macaques but is increasingly seen in suburban and urban populations. Further epidemiological studies are needed to fully understand the nature of the infection and its threats to humans in Southeast Asia. The potential of other primate species to act as reservoirs should be investigated and a Southeast Asian zoonotic malaria surveillance programme should be initiated to determine the epidemiology and spatial distribution of the infection among macaques in the region.

2.3.4 Distribution and abundance of vectors of knowlesi malaria in Sarawak Malaysia – Asmad Matusop and Rohani Ahmad

The general distribution of main vectors of knowlesi malaria in Malaysia was presented – An. cracens in Peninsular Malaysia, An. balabacensis in Sabah and An. latens in Sarawak.
The distribution and abundance of *P. knowlesi* vectors in Sarawak in 2015–2016 are shown in Fig. 5. **Fig. 5**: Distribution and abundance of *P. knowlesi* vectors in Sarawak, Malaysia, 2015–2016

*An. latens* is generally a forest species, commonly found in farming zones located at forest fringes rather than in villages, and their density decreases in relation to distance away from the jungle. A study by Tan et al. (2008) indicated that the relative abundance of *A. latens* in forests is 50% with sporozoite rate of 0.7%, 40% in farm areas with sporozoite rate of 1.4%, and 10% in longhouses with sporozoite rate of 0%. *An. latens* breeds almost exclusively in clear spring water in tiny seepages at the source of streams or along foothills in dense jungles. It is normally found in areas that are always under complete shade and not normally found in streams, swamps, paddy fields and irrigation channels. *An. latens* exhibits exophilic and acrodendrophilic behaviour, and it is simio-anthropophagic with a monkey-to-man biting ratio of 1:1.3. It is generally abundant during April-June and October–December. *An. latens* generally has the tendency to come out and bite at around 18:00, specifically in forests between 19:00 and 20:00, in farms between 01:00 and 02:00, and in longhouses between 23:00 and 02:00 (outdoor) and between midnight and 02:00 (indoor).

In Peninsular Malaysia, a study by Rohani et al. showed that the preferred breeding sites of *An. cracens* are ground pools, animal tracks and tyre tracks in recreational parks, fruit orchards, jungle fringes, and rubber and palm oil plantations. Most of the breeding sites are temporary pools, preferably small in sizes. *An. cracens* thrives in shaded and partially shaded areas with shallow water depth. It can live in clear or muddy water with low emergent plants. It prefers laying eggs in habitats more than 1 kilometre from human houses.

Most of the knowlesi malaria cases reported in Peninsula Malaysia were in rural villages, either near or bordering tropical forest fringes, and rubber or oil palm plantations. Commercial plantations tend to offer suitable environmental conditions for *Anopheles* mosquito breeding. Conditions as simple as wheel tracks containing enough water create perfect breeding sites for *An. cracens*. Clearly, people living and working in such plantation are most likely to be at risk for knowlesi malaria.

### 2.3.5 Does the current evidence indicate a possible change in *P. knowlesi* as human malaria? – Kamini Mendis

In the 2011 WHO Informal Consultation on the Public Health Importance of *Plasmodium knowlesi*, it was concluded that there is so far no evidence of human-to-human transmission of *P. knowlesi*. Natural human-to-human transmission (that is, the transfer of *P. knowlesi* from an infected person to another by mosquito vectors) has never been unequivocally demonstrated to occur in nature. It is clear that *P. knowlesi* can infect humans through mosquito inoculation as demonstrated experimentally, and
that such infections can also produce gametocytes. Early work (in the 1930s) showed that the first infections in humans produced few gametocytes, but after several (170) passages in humans, abundant gametocytes were produced. However, the infectiousness of such mosquito-induced infections to mosquitoes has not been explored, nor is it known if such mosquito infections can be infectious to humans.

The proof of principle that human-biting vectors that transmit human malaria can support the development of \textit{P. knowlesi} up to the infective sporozoite stage would require demonstration of infection in those vectors by membrane-feeding techniques and thereafter onward transmission to humans experimentally. This alone would, however, not constitute evidence that human-to-human transmission is occurring in nature.

The following categories of evidence would support the occurrence of human-to-human transmission in nature:

a. The presence of mixed infections of \textit{P. knowlesi} with human malaria species (\textit{P. falciparum}, \textit{P. vivax}, \textit{P. malariae}) in the mosquito vector (and, though less convincing, in humans). There is a single study conducted in Khan Phu, Viet Nam that reports finding gametocytes of \textit{P. knowlesi} in human infections as well as mixed sporozoite infections of \textit{P. knowlesi} and human malaria species in wild caught mosquitoes in the area (Maeno et al., 2017), supporting the possibility that human-to-human transmission is occurring in that area.

b. Demonstration of human blood (as opposed to simian blood) in mosquito vectors infected with \textit{P. knowlesi}. That is, this would require estimation of human blood index in vectors that transmit \textit{P. knowlesi}. The difficulties of capturing mosquito vectors of \textit{P. knowlesi} limit considerably the efforts to obtain such data.

c. Spatial and temporal microepidemiological studies. For example \textit{P. knowlesi} infection in a person with a contact history with a \textit{P. knowlesi} patient in an area without simian hosts, that is, the absence of close proximity to a simian reservoir. Such evidence has not been forthcoming so far.

d. Parasite genomics:
   i. Evidence of parasite selection by drug pressure in human \textit{P. knowlesi} isolates – for example, selection of mutations associated with drug resistance in \textit{P. knowlesi} infections as in the case of \textit{P. falciparum} – dihydrofolate-reductase (DHFR) mutants). A single study that investigated dihydrofolate-reductase mutations in human \textit{P. knowlesi} infections in Saba, Malaysia, found moderate diversity in the \textit{P. knowlesi} dihydrofolate-reductase (pdkhfr) gene, although there was no evidence that this reflected selective antifolate drug pressure in humans (Grigg et al., 2016b).
   ii. Demonstrating haplotypes in human infections distinct from those of parasites of simian infections (the selection of such unique haplotypes will, however, take a very long period of time).

Mixed infections of \textit{P. knowlesi} with human malaria parasites do occur in humans, and significant asymptomatic human reservoirs of human infections have been found.

Thus, some evidence points to the possibility of human-to-human transmission taking place, at least in some areas, but probably not very efficiently because of multiple reasons such as poor parasite adaption, size of human reservoir compared to the simian reservoir, and vector factors. Thus, human \textit{P. knowlesi} appears still to be largely a zoonosis. There is a need for research that is more directed at establishing human-to-human transmission. It should be noted that transmission dynamics are likely to change with time, if the incidence of human \textit{P. knowlesi} increases.

It was also noted that human-to-human transmission of \textit{P. knowlesi}, if it exists, has implications on the definition of malaria elimination and to WHO’s requirements in certifying countries as malaria-free. There is also a need to better understand other simian malaria species that may infect humans, such as \textit{P. cynomolgi} and possibly \textit{P. coatneyi}.
2.3.6 Transmission of *P. knowlesi*: Mathematical modelling study and potential implications for malaria control – *Chris Drakeley*

Disease transmission models are designed for large populations, homogenous mixing and homogenous biting. It assumes that rates and ratios are constant: for example, the ratio of mosquitoes to hosts is constant, mosquitoes feed and die at a constant per capita rate, mosquitoes take a constant ratio of their blood meals on a host species, and mosquitoes have a constant latent period. Models are useful, powerful and mathematically convenient, but they have limitations. Heterogeneity – for example, uneven distribution of bites amongst hosts – can be accounted for in standard models, but only to a certain extent. For *P. knowlesi* transmission, macaques are needed to be added in the model.

Three models were presented to determine *P. knowlesi* transmission. The first model considered habitat type (forest, farm, village) to show different areas of transmission. This model showed that human infection risk is highest when the macaque population is split or is moving between farm and forest habitats. This is consistent with the maintenance of *P. knowlesi* transmission by macaques in forest habitats and spill over into humans as macaques come into the farm. Only 1 of 1500 simulations of this model suggests human-to-human transmission, meaning this is infrequent but still possible. The second model looks into the environment where transmission is occurring to examine the likelihood of human-to-human transmission. This model showed that human-to-human transmission is possible in only 10 in 2000 scenarios (higher than model 1). The third model looks at examining what drives infection into a immunologically naïve population using vectors with varying degrees of human biting rate.

In summary, modelling shows that transmission is maintained primarily by high infection rates in macaques; human-to-human transmission is unlikely or rare; and longevity of the vector is critical for continued transmission. Modelling demonstrates that current control measures of long-lasting insecticidal nets (LLINs) and rapid treatment will work if actively implemented. Biting times of mosquitoes suggest additional, alternative approaches would be useful, for example community awareness, effective repellents, and sugar-baited traps for mosquitoes.

2.4 Technical session 4: Strategies for prevention and control

2.4.1 Susceptibility status of *P. knowlesi* vectors – *Rohani Ahmad*

A study by Rohani et al. on “Insecticide susceptibility status and resistance mechanism of *Anopheles cracens* Sallum and Peyton and *Anopheles maculatus* Theoald (Family: Culicidae) from knowlesi malaria endemic areas in Peninsular Malaysia” was presented. The study concluded that based on WHO adult mosquito bioassay, both *An. cracens* and *An. maculatus* showed some degree of resistance to malathion and dichlorodiphenyltrichloroethane (DDT). Only *An. maculatus* (Kampung Sokor) showed some degree of resistance to deltamethrin, while *An. cracens* are found to be susceptible. The study also showed that based on WHO larval bioassay, both *An. cracens* and *An. maculatus* showed some degree of resistance to malathion. Both, however, were susceptible to temephos.

2.4.2 Malaria surveillance and response practices in Malaysia and in particular relating to knowlesi malaria – *Jenarun Jelip*

The diagnostic approach of knowlesi malaria in Malaysia was presented. There were two flowcharts: a typical flowchart and a flowchart specifically for Sabah. In the typical flowchart, *P. falciparum*, *P. vivax* and *P. ovale* cases are quality-controlled, while *P. malariae* and *P. knowlesi* are automatically confirmed by PCR for final diagnosis. If there is a discordant diagnosis for *P. falciparum*, *P. vivax* and *P. ovale* after quality control, this is also confirmed by PCR before the final diagnosis. For Sabah, where *P. knowlesi* cases are high, the flowchart shows that all cases are automatically confirmed by PCR and quality controlled for final diagnosis. However, cases
determined as *P. malariae* or *P. knowlesi* in Sarawak are labelled as Pm/Pk and not all samples are subject to PCR assay due to limitations in laboratory capacity.

Malaria has been on the notifiable disease list of Malaysia since 1988. In 2010, this list was updated to include *P. knowlesi* cases as notifiable diseases. Two systems currently exist in Malaysia: e-NOTIFIKASI and eVEKPRO. e-NOTIFIKASI is a web-based system and accessible to all levels of health services in the country which registers all cases. If the case is confirmed for *P. knowlesi*, they have to also register at eVEKPRO, which registers malaria, chikungunya and other vector-borne diseases as well as outbreaks.

Malaria case investigation in Malaysia aims to confirm diagnosis, establish place of infection, conduct contact investigation, determine source of infection, determine onward transmission, establish onset of outbreaks, review treatment, conduct drug response surveillance and review control activities.

### 2.4.3 Current practices for prevention and control of *P. knowlesi* in Malaysia – Jenarun Jelip

Hunting, fishing, agriculture and logging activities are recognized as risk factors contributing to infection with knowlesi malaria. To increase awareness of communities, leaflets, billboards and other advocacy materials are produced and disseminated with assistance from relevant agencies to reach a wider audience, particularly high-risk groups. Hunters use Tuhau (*Etlinger coccinea*) as a natural mosquito repellent, as they do not want to use chemicals. Tuhau is from the ginger family and is commonly eaten either raw or cooked as a vegetable or as a condiment. Protective clothing (*baju berubat*) is also used commonly by forest goers and hunters.

### 2.5 Technical session 5: Programmatic actions to accelerate control

Below is a summary of the conclusions from discussions on each of the topics.

#### 2.5.1 Surveillance

In humans, *P. knowlesi* diagnosis should be confirmed by PCR. However, PCR protocols needs to be standardized. Thus, laboratories are encouraged to enrol in an EQA scheme for NAAT. Countries with *P. knowlesi* are requested to report *P. knowlesi* separately (not as *P. malariae*/*P. knowlesi* or non-*P. falciparum*). Also, case definition and investigation need to be standardized.

In primates and vectors, more information on primate infections with zoonotic species of *Plasmodium* and vector bionomics is needed, particularly information on what specific parasite(s) vectors carry. The linking of groups conducting studies on macaques and exploring the possibility of studying existing historically collected primate blood samples for presence of *P. knowlesi* will be useful. Primate and vector maps also need to be updated. Options discussed were exploring possible links with the Malaria Atlas Project and reviewing primate studies through the Malaria Eradication Scientific Alliance.

#### 2.5.2 Diagnosis

Identifying correctly the species has implications on case management. Thus, cases need to be confirmed by PCR as much as possible. If in areas where there is no microscopy or PCR, RDT with HRP2 may be used to exclude *P. falciparum*, but positives need to be referred to a hospital laboratory where microscopy or PCR is present.

#### 2.5.3 Treatment

Uncomplicated *P. knowlesi* should be treated with ACT and severe *P. knowlesi* with IV artesunate. However, there is a need to determine and define the criteria for severe *P. knowlesi*. During discussion, the following criteria were mentioned but these still need further research/investigation: age > 45
years, more than 10,000 parasites/µL (this is below the current recommendation of 15,000 parasites/µL), and the presence of abdominal pain. The current recommendation of CQ for prophylaxis against *P. knowlesi* among forest goers in Sarawak and Sabah also needs to be further evaluated for compliance and efficacy.

### 2.5.4 Vector control

Stronger health promotion on how to prevent infection from *P. knowlesi*, and where to seek diagnosis and treatment is recommended. Use of personal protective equipment (PPE), insecticide treated nets (ITNs) or indoor residual spraying (IRS) for prevention needs to be strengthened and further evaluated. Vector control efforts need to be aligned to the principles of integrated vector management.

### 2.6 Technical session 6: Research priorities

Below is a list of research priorities for *P. knowlesi*:

**Understanding the parasite**
- Virulence of *P. knowlesi* parasite
- Conduct genome sequencing and understand population genetics of parasites to standardize markers
- Collect more information on *P. knowlesi* prevalence and determine the burden of *P. knowlesi*
- In humans – better understanding on how *P. knowlesi* affects humans

**Laboratory diagnostics**
- Develop new RDT with antigenic proteins that can recognize *P. knowlesi*
- Determine extent of asymptomatic reservoir

**Entomology**
- Mapping of vectors and macaques; have better coverage of vector profiling
- Determine if vectors are incriminated – are they all capable of transmitting parasites (can be proved by PCR of vectors)?
- Determine if human movement has contributions on the transmission of *P. knowlesi*
- Determine if personal protective equipment is effective since *P. knowlesi* is an outdoor transmission
- Determine the need to check other zoonotic malaria aside from *P. knowlesi*, for example, *P. cynomolgi* and *P. coatneyi*
- Determine the most effective methods to control *P. knowlesi*

**Clinical management**
- Determine risk of *P. knowlesi* in pregnancy
- Determine the indicators for hospitalization
- Determine the prognostic indicators and the risk of death
- Determine if severity alone can be a predictor of death; high parasitaemia can determine severity but other indicators can also contribute to complications
- Determine if there is a value in shifting from IV artesunate to oral artesunate

**Surveillance and response**
- Distribution, hotspots, maps of cases, vectors, macaques
- Vector bionomics
- Determine if there is a vertical transfer or parasites in primates (congenital)

**Other areas**
- Determine if *P. vivax* protects *P. knowlesi* or if it glucose-6-phosphate dehydrogenase deficiency (G6PDd) that has protective effect on *P. knowlesi*
- Develop quantitative PCR for low-level parasite to predict prevalence of low parasitaemia (asymptomatic) using current assay
- Determine the evidence needed to know if there is human-to-human transmission.
3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

Malaysia still has the highest burden of \( P. \) \textit{knowlesi} (69\% of reported cases) with 2327 cases in 2016, particularly in Sabah and Sarawak. However, cases are also reported in Indonesia (465), the Philippines, Cambodia, Myanmar, Thailand and Viet Nam.

Early diagnosis of \( P. \) \textit{knowlesi} infection is important as severe \( P. \) \textit{knowlesi} malaria develops at lower parasite densities than with severe \( P. \) \textit{falciparum} infections, and therefore requires early aggressive management. Diagnosing \( P. \) \textit{knowlesi} using RDT and microscopy is difficult, and current confirmatory diagnosis is based on PCR. However, PCR tests must be standardized for quality assurance purposes and comparison of results.

Clinical trials conducted on the treatment of uncomplicated \( P. \) \textit{knowlesi} malaria showed that both chloroquine and ACTs (A-L and AS-MQ) are highly effective against \( P. \) \textit{knowlesi}, with ACTs providing faster parasite and fever clearance, thus earlier hospital discharge and lower usage of bed capacity. For the treatment of severe \( P. \) \textit{knowlesi}, retrospective studies showed that IV artesunate is effective. Prompt and accurate recognition of severe disease is vital.

Currently, there is no evidence of widespread human-to-human transmission. However human–mosquito–human transmission may be occurring in limited situations. Therefore, the meeting concluded that \( P. \) \textit{knowlesi} infection remains primarily a zoonotic infection, and identified the nature of evidence that needs to be sought by further investigating the possibility of human–mosquito–human transmission occurring.

Further research is needed on parasite epidemiology, virulence and population genetics; development of point-of-care diagnostic tools; distribution and mapping of cases, vectors and macaques; and clinical management. Specific research priorities include the following:

- Understanding the parasite: virulence of \( P. \) \textit{knowlesi} parasite; genome sequencing and population genetics of parasites to better understand parasite distribution in humans and macaques
- Laboratory diagnostics: development of new point-of-care RDT test to detect \( P. \) \textit{knowlesi} infection; determination of the extent of asymptomatic reservoir especially outside Malaysia
- Entomology: mapping the geographic distribution of vectors and macaques; determining most effective vector control methods that can control \( P. \) \textit{knowlesi} transmission
- Clinical management: determining the risk of \( P. \) \textit{knowlesi} in pregnancy; establishing parasitological density thresholds using IV artesunate to prevent development of severe \( P. \) \textit{knowlesi} malaria and reduce mortality.

3.2 Recommendations

3.2.1 Recommendations for Member States

1) Countries are encouraged to engage in research studies particularly on topics mentioned in the conclusions.
2) Laboratories conducting PCR for \( P. \) \textit{knowlesi} are encouraged to enrol in the WHO’s EQA scheme for NAAT.
3) Countries are urged to confirm \( P. \) \textit{knowlesi} cases through PCR. If in areas where there is no microscopy and PCR, RDT with HRP2 may be used to exclude \( P. \) \textit{falciparum}, but positives need to be referred to a hospital laboratory where microscopy or PCR is present.
4) Countries are encouraged to standardize case definition and investigation for \( P. \) \textit{knowlesi} and are requested to report on \( P. \) \textit{knowlesi} separately and not as Pm/Pk or non-\( P. \) \textit{falciparum}. 
3.2.2 Recommendations for WHO

1) Global guidelines on *P. knowlesi* are largely based on data from Malaysia. Since there is new evidence of wider geographic spread and different clinical manifestations, WHO is requested to consider these new data to guide revisions if necessary.

2) WHO is requested to support and provide technical guidance in conducting research studies mentioned in the conclusions.

3) WHO is further requested to determine relevance and implications of *P. knowlesi* infections to malaria elimination efforts in countries such as Malaysia.
REFERENCES


## AGENDA

### Day 1: Wednesday, 1 March 2017

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<tr>
<th>Time</th>
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<tr>
<td>09:00 – 09:30</td>
<td>Opening Session</td>
<td>Welcome address&lt;br&gt;Rose Nani Binti Mudin, Ministry of Health, Malaysia&lt;br&gt;Rabindra Abeyasinghe, Coordinator, Malaria, other Vectorborne and Parasitic Diseases, WPRO/WHO&lt;br&gt;Meeting objectives&lt;br&gt;Self-introduction of participants and observers&lt;br&gt;Administrative announcements&lt;br&gt;Glenda Gonzales, Technical Officer, WPRO/MVP</td>
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<td>09:30 – 10:00</td>
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<td>10:00 – 10:10</td>
<td>Session 1: Epidemiological review of knowlesi malaria</td>
<td>Introduction to the Regional Action Framework for Malaria Control and Elimination in the Western Pacific 2016-2020, the importance of addressing the challenge of knowlesi malaria&lt;br&gt;Rabindra Abeyasinghe</td>
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<td>10:15 – 11:00</td>
<td>Session 1: Epidemiological review of knowlesi malaria</td>
<td>Overview of <em>P. knowlesi</em> malaria&lt;br&gt;Epidemiology of <em>P. knowlesi</em> in Malaysia–detection, surveillance, its host &amp; vectors and spatio-temporal distribution and trends&lt;br&gt;<em>P. knowlesi</em> malaria in other countries&lt;br&gt;Rose Nani binti Mudin, Kevin Baird</td>
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<td>11:00 – 12:00</td>
<td>Session 1: Epidemiological review of knowlesi malaria</td>
<td>Updates on <em>P. knowlesi</em> malaria&lt;br&gt;- Parasites, what do we know?&lt;br&gt;- Vectors, principal vectors, their bionomics&lt;br&gt;- Patients – who is affected?&lt;br&gt;- Zoonotic reservoirs - macaques&lt;br&gt;Balbir Singh, Indra Vythilingam, Nicholas Anstey, Reuben Sunil Kumar Sharma</td>
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<td>12:00 – 13:00</td>
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<td>13:00 – 13:30</td>
<td>Session 2: Diagnosis and Clinical Management</td>
<td>Laboratory Diagnostics for <em>P. knowlesi</em>&lt;br&gt;Malaria Microscopy, NAAT for the detection of human infections with <em>P. knowlesi</em>&lt;br&gt;Balbir Singh</td>
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<td>Session 2: Diagnosis and Clinical Management</td>
<td>Development of (field-based/point-of-care) diagnostic tools for <em>P. knowlesi</em>&lt;br&gt;Lau Yee Ling</td>
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<td>Discussion&lt;br&gt;All</td>
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<td>14:00 – 14:45</td>
<td>Session 2: Diagnosis and Clinical Management</td>
<td>Updates on clinical management of knowlesi malaria, optimum treatment regimens&lt;br&gt;Timothy William</td>
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<td>Discussion&lt;br&gt;All</td>
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<td>15:15 – 16:15</td>
<td><strong>Session 3:</strong> Evidence review of human-to-human transmission of P. knowlesi</td>
<td>Is human-to-human transmission of <em>P. knowlesi</em> a possibility – laboratory evidence</td>
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<td>Epidemiology and spatial distribution of <em>P. knowlesi</em> infecting macaques in Peninsular Malaysia</td>
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<td>Distribution and abundance of vectors of <em>P. knowlesi</em> malaria</td>
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<td>Does the current evidence indicate a possible change in <em>P. knowlesi</em> as human malaria?</td>
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<td>Introduction of new international EQA scheme for NAAT methods</td>
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<td>Transmission of <em>P. knowlesi</em>: Mathematical modelling study (2014 study) and potential implications for malaria control</td>
<td>Transmission of <em>P. knowlesi</em>: Mathematical modelling study (2014 study) and potential implications for malaria control</td>
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<td>Malaria surveillance and response practices in Malaysia and in particular relating to knowlesi malaria</td>
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<td>Rabindra Abeyasinghe</td>
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