Webinar Q&A

Forest-goers and residual malaria: Addressing the Challenge

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Panelists

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Question	Are there lessons to be learnt from South America (especially Amazon area) and vice versa? *From Ian Burton*
Dr Bill Hawley	I listened last week to a webinar on the topic given by PAHO. There are indeed many similar challenges, including the need to decentralize elimination activities. I agree we could learn much from each other.
Dr Jeffery Hii	As there are similarities between PAHO and SEARO/WPRO countries, we could use APMEN VCWG, SRWG and ORENE platforms for exchange of experiences and learnings. The greatest proportion of malaria in the Americas is located in the Peruvian and Brazilian Amazon Basin. Of the 143 500 malaria cases recorded in Brazil in 2015, 99.7% of them were acquired in the Amazon Basin. Information about ongoing malaria transmission in two different hotspots in the Peruvian and Brazilian Amazon, see http://vbd-environment.org/residual-malaria-hotspots-in-peru-and-brazil in GMS countries of Thailand and Vietnam, see http://vbd-environment.org/residual-malaria-transmission-in-thailand-and-vietnam

	and in Papua New Guinea see http://vbd-environment.org/papua-new-guinea-study Through the E-2020 Initiative, PAHO has 21 countries with the potential to eliminate malaria by 2020 and Paraguay was certified malaria-free (https://www.who.int/news-room/detail/11-06-2018-who-certifies-paraguay-malaria-free, WPRO has a target of 3 countries to achieve elimination by 2020. https://iris.wpro.who.int/handle/10665.1/13578 SEARO's elimination target is at least two of the nine malaria endemic countries by 2020, at least five of the nine by 2025, and all nine by 2030 https://apps.who.int/iris/bitstream/handle/10665/272389/9789290226253-eng.pdf?ua=1
Dr Indra Vythilingam	Yes I agree with Bill it will be good for countries involved to voice out so that we can be heard and can move forward

Question	What is the definition of residual malaria? Why is knowlesi malaria considered residual malaria? It is transmitting while vivax and falciparum malaria still exist. *From Jonathan Wee Kent Liew*
Dr Bill Hawley	While not officially on the WHO list of parasites to be eliminated, given the amount of morbidity and mortality is causes, it most certainly qualifies as 'residual malaria' in the operational sense in both Malaysia and Indonesia, as both governments are trying to figure out how to at least minimize its impact.
Dr Jeffery Hii	The 2014 definition of residual malaria transmission (https://www.who.int/malaria/publications/atoz/guidance-control-residual-transmission/en/is replaced by "Persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme" see WHO Malaria terminology (last update: June 2018). Knowlesi malaria is a good example of persistent (ongoing) malaria transmission despite Government's efforts to maintain high (or universal) coverage of vector control, access to health services in space and time.
Dr Indra Vythilingam	knowlesi is not typically thought of residual malaria. But in my personal view, it ought to be thought of in that category, as indeed governments will have to deal with it.

Question	Who will do LSM in deep forest and unreachable areas? Any possibility for Malaria elimination *From Rs Sharma*
Dr Bill Hawley	Probably not possible in deep forest. Repellents, LLINs, insecticide treated clothing, VMWs probably a better bet in such environments.
Dr Jeffery Hii	Generally, larvae of forest vectors develop better in bodies of water under tree canopy where the water temperature is buffered and usually 3–3.5oC lower than that of sun-exposed bodies of water. LSM is not possible in forested settings due to the significant resources and effort required to locate, identify and treat small, clear and multiple stagnant bodies.
Dr Indra Vythilingam	One also needs to understand that these people who go into to the forest are mostly poor people and they will not be able to afford repellents etc.

	Some help should be provided to these people. Perhaps a light weight treated loose overcoat may be able to prevent mosquito bites

Question	**To Dr Bill Hawley**: Could you further detail what you meant by 'putting pressure on gametocytes'? Was there a specific transmission blocking treatment or early detection leading to reduced gametocytemias? *From Andrea Ruecker* **A follow-up: Thank you. Pv form gametocytes were quickly and symptomatic Pf patients already have gametocytes (often still sequestered) by the time they attend the clinic or VMW. Hence, I wonder how early detection would help to reduce the already committed gametocytes (in often already mature in case of Pf)? Thanks again.**
Dr Bill Hawley	If diagnosis and treatment are delivered quickly, then ***some*** parasites can be killed before gametocytes are formed. thus, VMWs can assist in reduction of transmission by more quickly killing parasites before gametocytes are formed. Speed is the essence. Response to follow up: we don't know how much early detection will reduce transmission, but data from Myanmar suggest that deployment of VMWs does have an impact. The idea is to deploy multi imperfect transmission-reducing interventions to increase the probability that the parasites will go locally extinct. I added a modifier in red, above, to clarify my initial response.

Question	What kind of Hammock nets (brand, AI) do you use for the forest-goers in SEA countries? *From **Chris Daeyun Kim***
Dr Bill Hawley	I think Dr. Hii may have addressed this in his talk. Please refer to Dr Hii's presentation.
Dr Jeffery Hii	Hammocks are popular and widely used in Cambodia, Laos and Vietnam. WHO Prequalified hammock nets are derived from treated netting and marketed by Vestergaard, Tianjin Yorkool International Trading Co Ltd and Fujian Yamei Industry which have production facilities for WHO-PQ products in Asia Pacific. Accessed at https://www.who.int/pq-vector-control/prequalified-lists/en/. They are referred as Long-Lasting Insecticidal Hammock Nets (LLIHNs).
Dr Indra Vythilingam	In Malaysia people are not used to hammocks, so we need to think of some other methods

Question	**To Dr Bill Hawley:** The question is to know the cost effectiveness for LSM because in rural areas it goes beyond limit for malaria vectors for Dr Hawley *From Dr Pradeep Srivastava*
Dr Bill Hawley	That's hard question to answer, as the it will be dependent upon larval habitat characteristics. One thing to consider is that in elimination contexts, LSM should be time limited and might be discontinued after

	elimination is achieved. This consideration changes the cost-effectiveness calculation considerably.
Dr Jeffery Hii	The cost per person protected per year (pppy) depends mainly on: (1) the type of formulation required for treating different aquatic habitats, (2) the human population density relative to the density of aquatic habitats and (3) the potential to target the intervention in space and/or time. In Africa, costs for LSM compare favourably with costs for IRS and LLINs, especially in areas with moderate and focal malaria transmission where mosquito larval habitats are accessible and well defined (Worrall E et al Malaria J 2011; 10: 338. Larviciding was shown to be cost-effective in Tanzania for incidences as low as 40 infections per 1,000 people per year (Maheu-Giroux et al Malaria J 2014; 13: 477.
Dr Indra Vythilingam	In forested areas LSM is not feasible. To be honest I find it very difficult to find breeding sites. Thus I thought if I can find resting sites it would be useful, but unfortunately have never been successful in collecting resting mosquitoes even in Sabah where the vector density is high.

Question	Thank you very much for presentation. Jhum cultivation is shifting cultivation, is common in north eastern states in India particularly in Tripura., where malaria is highly endemic. This is important risk factors, that needs to be also addressed. Regarding best practices of PPP in Indonesia. Are these best practices using by national malaria program in Indonesia? *From Roop Kumari*
Dr Bill Hawley	Private public partnership with some of the larger gold mines and plantations are in effect, and have been encouraged and facilitated by the NMCP. Expansion of such efforts to less formal sectors is a challenge, however.
Dr Jeffery Hii	The two large mining companies operating in Indonesia – Freeport Papua and Amman Sumbawa adopt integrated workforce and community resources, complementary objectives between stakeholders for health improvements in affected communities, data exchange, capacity building, basic and operational investigations, and shared goals. Industry contributions especially in remote locations maximize unique opportunities for meeting collective goals and mutual long-term, productive collaborations. Extractive industry (e.g. mining companies) are good examples of "Best Practice" as their CSR policies and guiding principles assist development among 'affected ' communities. Consequently, productivity is maximized by reducing impact of disease on workforce; reduction in health costs (curative and preventive) and recruitment of talent and experience.

Question	Are you saying in your conclusion that we can eliminate malaria in SE Asia without the malaria vaccine? Or without any new tools? *From Dr Win Han Oo*
Dr Bill Hawley	Yes, I think it is possible without a vaccine. Sri Lanka showed the way for much of the region. However, lowland Papua will be a challenge.

Dr Jeffery Hii	In the Western Pacific region, 4 countries: Taiwan, Australia, Singapore, and Brunei were declared malaria-free in 1965, 1981, 1982 and 1987 respectively, WITHOUT a malaria vaccine and after meeting the WHO assessment of having 1) a comprehensive and efficacious case detection mechanism; 2) reliable microscopic diagnosis of blood smears; 3) thorough epidemiological investigations and a satisfactory epidemiological situation; 4) adequate preventive and remedial actions upon detection of cases; 5) adequate general health services, effective system of case notification, and epidemiological follow-up for prevention of re-establishment of malaria. See https://www.who.int/malaria/areas/elimination/malaria-free-countries/en/
Dr Indra Vythilingam	My fear is that when malaria is eliminated, health staff will forget PK and other simian malaria exist, thus there might be more death due to these malarias. I feel that something must be done for simian malarias.

Question	Can you please explain the hurdles that south east Asian countries is facing due to COVID 19 especially delay in malaria elimination? *From Amreen Ahmad.* Note: This question was answered live by the panelists. Please feel to provide responses if you'd like.
Dr Bill Hawley	Two big challenges: 1. Procurement of PPE and logistics to supply to health workers and 2. Fear in the community and in health workers leading to deterioration of programs.
Dr Jeffery Hii	Impacting global health product supply chains; affecting manufacture, distribution and demand/supply dynamics. Countries will face interruption in supply chain of antimalarial drugs, rapid diagnostics tests, chemicals for IRS and bednet treatment. The market for RDTs of Covid-19 is more lucrative compared to malaria RDTs. For more information, contact Dr Leo Braack for APMEN webinar talks (15 May 2020) on "Sustaining malaria services during a pandemic: What do we need to do?" and PPT presentations on "Maintaining malaria operations in the context of COVID-19" by Drs Neena Valecha (SEARO) and James Kelly (WPRO) and "Challenges of malaria service delivery during Covid-19 by Dr Rose Nani Mudin.

Question	Could you explain in detail with the VMW can do for malaria elimination in terms of entomology activities? *From Sokny Mao*
Dr Bill Hawley	Hi Sokny, that's a good question. They can assist with advocacy for LLIN and hammock use. They may also assist with mapping of larval habitats.
Dr Jeffery Hii	Advocate for forest goers from their community to bring forest packs with LLIHNs or repellents to farm huts and forest plots and share information with OD authorities. Including replacement of expired LLIN/LLIHNs and care and maintenance of torn bednets and hammock nets.
Dr Indra Vythilingam	Also search for the resting places of these mosquitoes

Question	Please speak to the topical repellent trial in Myanmar *From Michael Macdonald*

	Note: This question was answered live by the panelists. Please feel to provide responses if you'd like.
Dr Bill Hawley	
Dr Jeffery Hii	Based on non-final analysis (NFA) there was an approximate 75% average reduction in the odds of Plasmodium spp. infection in villages after transitioning from no-repellent to repellent distribution by VHV [from a poster by Agius PA et al "**Effectiveness of repellent delivered through village health volunteers on malaria incidence in villages in South-East Myanmar: a stepped-wedge cluster-randomised controlled trial,"** Poster presentation at World Malaria Congress, Melbourne, Australia, 1-5 Jul 2018. Conclusions and future directions: "a) Large scale implementation of a mosquito repellent distribution program and associated data collection is achievable/feasible; b) Malaria incidence declined over the study period, independent of seasonality and any effect of repellent - Further analyses will include malaria detected by PCR; c) Considerable heterogeneity in malaria incidence and the effect of repellent distribution was observed and should be accounted for in future research; d) Community acceptability and feasibility to implement repellent should be tested by further operational research for the communities where the repellent is planned to be implemented as a programmatic tool. Also see Win Han Oo et al "Effectiveness of repellent delivered through village health volunteers on malaria incidence in villages in South-East Myanmar: a stepped-wedge cluster randomised controlled trial protocol" BMC Infectious Diseases (2018) 18:663; https://doi.org/10.1186/s12879-018-3566-y
From Audience (Win Han Oo)	We have implemented it https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6295052/ Will publish the findings soon.

Question	**To all speakers**: Malaria elimination is the biggest challenge in the Islands Indonesia, where there are many breeding places for malaria that will break out if there is development land and seasonal workers. hope for best solution eliminate that. *From Ardani Akhirudin*
Dr Jeffery Hii	Indonesia has a long history of successful environmental management for malaria control {Takken W, et al 1990) Environmental measures for malaria control in Indonesia: an historical review of species sanitation. Wageningen Agricultural University Papers 90. 7, 1– 167. This should be continued and expanded. Community driven vector control funded with Global Fund should use participatory approach such as PLA (Participatory Learning and Action) to encourage communities to reduce transmission risk further via environmental modification and increased personal anti mosquito practice. The Government of Indonesia since the last five years have been providing cash assistance to villages (village fund) in the country to be used for village development agenda as agreed by the village members. The malaria PLA (participatory learning and action) will

	trigger the community to use the village fund to perform community vector control activities.

Question	To Dr Bill Hawley: Regarding your last comment on the cost of vector control, what do you think about the use of spatial repellent in forest ? *From **Sébastien Boyer***
Dr Bill Hawley	Worth trying in forest camps, though we'd want a product that lasts long and is robust when exposed to rain and heat. Private sector is working on it.
Dr Jeffery Hii	Whilst novel spatial repellents are effective in indoor environments, they do not perform equally well in outdoor or forest settings. Trials with metofluthrin-impregnated plastic strips for mosquitoes present in shelters without walls (beruga) carried out in Lombok, Indonesia showed a major reduction in the incidence of human biting by Culex quinquefasciatus; the use of two strips per beruga repelled >60% of the mosquitoes for at least 11 wk while 4 strips repelled >60% of the mosquitoes for more than 15 weeks [Kawada H et al J Vector Ecol. 2005; 30:181–5]. In a forested village in Cambodia, landing rates of mosquitoes were reduced by 48% by a single metofluthrin emanator and by 67% by four emanators. Whilst equivalent reductions were seen among mosquito species collected in Pursat, however, in Koh Kong, the use of four metofluthrin emanators had no demonstrable effect on landing rates (Charlwood JD et al. Med Vet Entom 2016; 30: 229–234). This could be due to pyretrhoid resistance, low mosquito densities and under0-powered study design. These findings suggest that although the product can produce a significant effect, it requires further improvement.
Dr Indra Vythilingam	Should study transfluthrin's efficacy

Question	The problem with repellents is compliance. What about spatial repellents? *From John Invest - Sumitomo UK*
Dr Bill Hawley	There are devices which work outdoors and there is `Clip On` which the persons wears and has a small fan.
Dr Jeffery Hii	For spatial repellents, we'll need robust products that can withstand the elements. To date, spatial repellents have been aimed at the indoor environment, whereas I hope we'll have products that might be used in forest camps in remote outdoor forested areas. A recent feasibility and acceptability study in Mondulkiri, Cambodia showed that spatial repellents were well received in villages, although 63.2% of respondents would not replace bed nets with repellents. Most participants (96.6%) were willing to use the product again; the mean willingness to pay was US$ 0.3 per unit. It was concluded that "widespread use of spatial repellents would not fill all protective gaps, but, if their entomological efficacy could be ascertained, outdoor application has the potential to enhance vector control strategies. Successful implementation would require subsidisation and integration with the existing national malaria control strategy" (Liverani M et al Malar J 2017; 16: 412).

Dr Indra Vythilingam	How good is transfluthrin is outdoor areas? Material treated with transfluthrin and hung around the place to keep away the mosquitoes- should be investigated

Follow-ups:

- They are expensive metafluthrin was tested in Cambodia but eventually sumitomo said it was never intended for malaria control.
- I work for Sumitomo and that is not entirely true. Willingness to pay is perhaps the problem as metoflutrin is not as cheap as LLIN

Question	**To Dr Bill Hawley**: Regarding the last comment on use of New tools - Some tools are innovative and new in nature but do not have a WHO PQ listing, like Insecticide Treated Screens. There is evidence from Lab and also from agriculture use that shows effectiveness against different vectors. Should we wait to deploy such tools? *From Maneesh Sharma*
Dr Bill Hawley	It is a country by country decision, but they'll have to use their own funds to procure.
Dr Jeffery Hii	Novel and innovative tools that do not have a WHO PQ listing will need a efficacy data and Concept of Proof supported by SFS, small scale entomological and safety studies and/or large-scale epidemiological impact trials – for classification of intervention class and prototype/products under VCAG review; see http://www.who.int/vectorcontrol/vcag/en/.

Question	To Dr Jeffery Hii: I have one question to Dr Jeffrey Hii. What do you think practicing thermal fogging to reduce malaria vector population in knowlesi-prone localities? Is it effective? *From **Nur Syafiqah Nasir***
Dr Bill Hawley	Totally agree with Jeffery, These areas are even hard to access by foot. Large forest areas.
Dr Jeffery Hii	It depends on access and logistics involved in transporting insecticides and fogging equipment to forested areas where there is no clear pathways or road signs. It's very challenging task and one without risks.
Dr Indra Vythilingam	I am not sure how effective fogging is going to be. I also need to realize that we will be killing lots of beneficial insects as well

Question	To Dr Jeffery Hii: Jeffrey Thanks a lot for nice presentation. What was level of active surveillance in terms of satisfactory blood examination rate and also what was ratio between active and passive surveillance behind success story. *From Pradeep Srivastava*
Dr Jeffery Hii	Hi Pradeep I am waiting the response from the Indonesian authorities as I don't have this at the moment

Question	General comment and question - which relates to a few comments on the chat and links to Jeffrey's presentation. One of (if not THE) key challenges

	is understanding the financial flow (i.e. who pays for the tools). If Global Fund or other major international funders are involved it is unlikely that a product which does not have PQ listing will be supported. However national or domestic funding creates greater flexibility (as illustrated with the forest pack from Cambodia) - of course the ultimate flexibility is consumer choice - but the distribution channel becomes more complex and there are more mouths to feed in the distribution steps. Question therefore - how we do encourage greater recognition of national registration programs and greater engagement of domestic funding towards addressing residual transmission - which is probably more realistic than seeing PQ listed products supported by GF and other international donors. *From Justin McBeath*
Dr Bill Hawley	I believe VCAP (of APMLA) are focusing efforts on national regulators thru' information sharing and capacity building. Greater engagement of domestic funding is encouraged by Global Fund modality of funding in the recent Window 1 and 2.
Dr Jeffery Hii	- The forest packs in Cambodia are supported by GF and NOT procured with domestic financing. The need to strengthen local regulatory pathways is not separate from WHO-PQ systems, as the national pathways in the region should ideally be harmonized with best practices outlined by WHO-PQ. As APMLA VCAP site is currently developed to show country-specific 'vector control access' roadmap for APLMA's Access team (work in progress), you could access the IVCC regulatory pathway report which John Paul nicely did last year. Among the 5 application approaches for the 2020-2022 Allocation Period, GF has a "Tailored for Transition" strategy which is suitable for countries approaching transition from GF financing which are building sustainable programs with decreasing Global Fund support. https://www.theglobalfund.org/media/8608/fundingmodel_2020-2022cycle_faq_en.pdf. In addition GF has a 3rd strategic objective "Implement and partner on market shaping efforts that increase access to affordable, quality-assured key medicines and technologies, see p35 attached, quoted below:

Question	What activities are supposed to be under medical anthropology? *From Ye Hein Naing*
Dr Bill Hawley	What the immunizations people would call 'demand creation' -- treatment seeking and use of personal protection is an important field of medical anthropology.
Dr Jeffery Hii	Medical or social anthropologists identify and described concerns and understandings of disease, including local knowledge of cause and treatment relevant to disease control. They translate these local concerns into appropriate health interventions, for example, by providing information to be incorporated in education and communication strategies for disease control. They also translate local concepts of illness and treatment; adapt biomedical knowledge to fit local aetiologies; and examine the local context of disease diagnosis, treatment and prevention,

	and the structural as well as conceptual barriers to improved health status.

Question	To Dr Jeffrey Hii: Has there been research in different areas of the Mekong to assess acceptability of using hammock nets in the forest goer populations? And, post distribution, assessing the whether the hammock nets are used every night and replaced when they're broken? Thanks. *From Julia Dunn*
Dr Jeffery Hii	Not much I am afraid. Very few studies have assessed acceptability and preference of treated bednets; e.g. Xu et al Use of Bed Nets and Factors That Influence Bed Net Use among Jinuo Ethnic Minority in Southern China. PLoS ONE 9(7): e103780; Dysoley L et al Assessment of net lending strategy to better reach mobile and migrant populations in malaria endemic areas of Cambodia. Infect Dis Poverty. 2018; 7: 107; Gryseels C et al A Critical Enquiry into Variability of Insecticidal Net Use in Cambodia: Implications for Assessing Appropriateness of Malaria Elimination Intervention. Am. J. Trop. Med. Hyg., 2019; 100: 1424–1432

Question	very nice presentation Dr. Jeffrey, LLINs are really good option , however other impregnated clothing like socks, gloves, hoods and ITCs can also be considered as personal and community protection methods. *From NEERA KAPOOR*
Dr Jeffery Hii	Insecticide Treated Clothing (ITC) and personal wearables are a cost-effective strategy as they require minimal behavioural change and communication. Recent studies in Thailand and Myanmar showed high acceptability for insecticide-treated school uniforms for dengue prevention [Murray N et al Acceptability of impregnated school uniforms for dengue control in Thailand: a mixed methods approach. Glob Health Action. 2014; 7:24887] and permethrin-treated long clothing worn for malaria prevention [Crawshaw A et al Acceptability of insecticide-treated clothing for malaria prevention among migrant rubber tappers in Myanmar: a cluster-randomized non-inferiority crossover trial. Malaria J 2017; 16: 92]. Providing communities with personal protective tools that take into account their practices and preferences and are tailored to purpose (e.g. protection specifically during rubber tapping) are needed to target the gaps which traditional core measures cannot reach.

Question	What is radical treatment for P. knowlesi? *From Rs Sharma*
Dr Jeffery Hii	"Plasmodium knowlesi occurs across Southeast Asia and is the most common cause of malaria in Malaysia. High parasitaemias can develop rapidly, and the risk of severe disease in adults is at least as high as in falciparum malaria. Prompt initiation of effective treatment is therefore essential. Intravenous artesunate is highly effective in severe knowlesi malaria and in those with moderately high parasitaemia but otherwise uncomplicated disease. Both chloroquine and artemisinin-combination

	therapy (ACT) are highly effective for uncomplicated knowlesi malaria, with faster parasite clearance times and lower anaemia rates with ACT." Barber BE et al The Treatment of Plasmodium knowlesi Malaria. Trends in Parasitology 2016, 33: 242-253.
Dr Indra Vythilingam	ACT is fine.

Question	I am Semuel from Papua, what the good vector control for An. farauti complex in high land geographic and costal geographic. *From Semuel Sandy*
Dr Bill Hawley	For coastal areas, drainage of lagoons might be possible. Highlands are difficult, though
Dr Jeffery Hii	The near-universal distribution of LLINs and an infusion of money for diagnosis and treatment of malaria (GF grant of US$ 109 million in 2009 and guided by WHO's technical recommendations), PNG distributed more than 7.5 million nets during the following 6 years. The effort has slashed the incidence of malaria in PNG since 2004, from 400 cases per 100 000 population to 200. Between 2009 and 2015, the incidence of malaria admissions to public health facilities dropped by 83%, and malaria death rates in health facilities fell by 76%. https://www.who.int/news-room/feature-stories/detail/despite-overwhelming-challenges-papua-new-guinea-has-made-major-strides-against-malaria. Bednets are not the only interventions credited for the advances; surveillance, diagnosis and treatment also play roles in prevention. Surveillance helps planners identify where to distribute bednets, and treatment of individuals prevents other cases from occurring,

Question	How to detect the sporozoite rates by dissection on the head? *From Sokny Mao*
Dr Indra Vythilingam	Under the light microscopes, we can observe the sporozoite in salivary glands. It is always good to dissect mosquitoes, examine the ovaries- for parous rate, gut and gland for oocysts and sporozoite

Question	Please clarify 3-6 meters while you were describing biting time. *From Raghavendra*
Dr Jeffery Hii	To know if the mosquito is biting at the ground level, or 3-6 meters above ground, mosquito collection is carried out on the ground, and on platforms 3-6 meters above ground.
Dr Indra Vythilingam	3-6 meters high above the ground. This is also one of the methods to determine the preference of the mosquitoes- biting humans or monkeys. It can be determined by blood meal analysis but unfortunately we have problems collecting resting mosquitoes

Follow ups

- expected proportion of pk malaria, if any
- Platform built at 3methers and 6 meters high for the monkey baited traps

Question	To Dr. Indra Vythilingam: Thank you for your presentation: I am a very big ban of your works. I think that if you begin to trap before 6 pm, you can catch mosquitoes before, and also during day time, especially in forest.
Dr Indra Vythilingam	I am not sure we usually sit around earlier than 6 or 7 depending on the site but we notice that the first mosquito comes at 7.20 pm sharp. We also had problem collecting resting An. balabacensis we don't know where they are resting

Follow ups:

- Thank you very much. If you have time and people, it could be interesting to catch during 24 hours :) Thanks again for your presentation and the huge amount of work you already do for Medical Entomology.

Question	To Dr. Indra Vythilingam: Does ACT cure siminan malaria? *From Prudence Hamade*
Dr Bill Hawley	
Dr Jeffery Hii	Yes, it does. "High parasitaemias of P knowlesi can develop rapidly, and the risk of severe disease in adults is at least as high as in falciparum malaria. Prompt initiation of effective treatment is therefore essential. Intravenous artesunate is highly effective in severe knowlesi malaria and in those with moderately high parasitaemia but otherwise uncomplicated disease. Both chloroquine and artemisinin-combination therapy (ACT) are highly effective for uncomplicated knowlesi malaria, with faster parasite clearance times and lower anaemia rates with ACT." Barber BE et al The Treatment of Plasmodium knowlesi Malaria. Trends in Parasitology 2016, 33: 242-253.
Dr Indra Vythilingam	It works well for knowlesi, the 2 cases of cynomolgi malaria were also treated with ACT.

Question	How serious clinically is P Knowlesi? *From John Invest - Sumitomo UK*
Dr Bill Hawley	
Dr Jeffery Hii	You can die if not treated early. "High parasitaemias of P knowlesi can develop rapidly, and the risk of severe disease in adults is at least as high as in falciparum malaria. Prompt initiation of effective treatment is therefore essential. Intravenous artesunate is highly effective in severe knowlesi malaria and in those with moderately high parasitaemia but otherwise uncomplicated disease. Both chloroquine and artemisinin-combination therapy (ACT) are highly effective for uncomplicated knowlesi malaria, with faster parasite clearance times and lower anaemia rates with ACT." Barber BE et al The Treatment of Plasmodium knowlesi Malaria. Trends in Parasitology 2016, 33: 242-253.
Dr Indra Vythilingam	Can cause death. In Borneo about 8-10 years ago, severe knowlesi malaria can occur about 1 in 10 cases, if not treated fast.

Question	Would mosquito monitoring and surveillance be improved by new and better tools? *From Richard Adey*
Dr Bill Hawley	

Dr Jeffery Hii	Cow-baited tents are highly effective in sampling diverse Anopheles malaria vectors in Cambodia. This sampling method captured high numbers of anophelines with limited sampling effort and greatly reduced human exposure to mosquito bites compared to the gold-standard human landing collection. Malaria J 15: 440 (2016). As cattle is usually absent in forested areas (which are not their natural grazing or resting habitat), we need better and sensitive mosquito monitoring tools.
Dr Indra Vythilingam	For Anopheles surveillance we now need new tools as we know that they are biting outdoors and early. We don't know where they are resting. Setting up resting buckets to collect Anopheles did not work although it works in Africa. We have a big challenge ahead of us. The best method is still HLC and is getting more difficult.

Question	Although It is not found the evidence yet for the human-human knowlesi transmission, up to your idea knowlesi could be new human parasite soon? *From Sokny Mao*
Dr Indra Vythilingam	The way forward it will be. If many people are screened for malaria parasites by molecular tools I am sure we will find many cases than reported

Question	To all speakers: Are the current drugs and diagnostics are adequate to manage simian spp esp knowlesi which will become more important as falciparum and vivax are eliminated? Is there enough R&D focus on developing necessary new tools? Where are the gaps? *From Ian Boulton*
Dr Bill Hawley	Knowlesi responds to currently used drugs - it is particularly susceptable to pyrimethamine for example. Gaps are in point-of care diagnostics. WEereally need a good, specific RDT for knowlesi. THere is some work on LAMP for this purpose too. We need something cheap and easy to use.
Dr Jeffery Hii	As Pk malaria parasites are sensitive to chloroquine and ACT drugs, there are no barriers to treatment. What is important is early diagnosis and treatment - which requires robust health systems. There is not much R&D on personal protection tools and there is a big gap here.
Dr Indra Vythilingam	I agree on need for RDTs. My concern is that drug resistance can catch us out and time to develop new drugs. Should we be up-rating the urgency of working on a range of anti-knowlesi drugs with a range of modes of action.

Follow ups:

- Drug resistance is not (currently) a major concern with Pk. This is because the major pool of parasites circulates in monkeys, who are not exposed to drugs. It is thought unlikely that drug resistance will appear in Pk. Agree with Dr Hii that we need to think about PPT for forest workers.

Question	What time in daytime do you get biting by An dirus ? *From Ipsita Pal Bhowmick*
Dr Bill Hawley	
Dr Jeffery Hii	About 20% of daytime biting by Anopheles vectors occur in forested areas of Cambodia (Amelia Vantaux, Institute Pasteur Cambodge). Biting by An dirus can happen in daylight in the jungle [Klein JM. La faune des moustiques du Cambodge. Cahiers de l'ORSTOM – série Entomologie

	Médicale et Parasitologie. 1977, XV: 107-122; Rosenberg R et al Forest malaria in Bangladesh. II. Transmission by Anopheles dirus. Am J Trop Med Hyg. 1982, 31: 183-191].

Question	**To Dr Jeffery Hii***:* Is the current guidance from WHO on larvaciding and larval control a hindrance to the strategy that you were advocating for east of Wallace line? *From Ian Boulton*
Dr Bill Hawley	Actually, I was hoping former WHO scientist Jeffrey would answer this question, but I see he has given it to me. 😊 WHO has a challenge in crafting global guidance that may not adequately reflect reality in particular areas. The 'fixed few findable' mantra was developed in reaction to efforts to expand LSM directed against An gambiae in Africa; this may have had an inhibiting effect (I am speculating – no quantitative data) on scale up of LSM in parts of Asia, which has longer experience with this approach. Every intervention has its advocacy group; my hope is that programs will adopt practical and effective local solutions incorporating multiple interventions. In elimination contexts, clear-cut epidemiological evidence is sometimes not available.
Dr Jeffery Hii	This question is best answered by Bill

Question	Providing repellent to the communities of forest goers would be very expensive to the programme? *From Tobgyel Tobgyel*
Dr Bill Hawley	
Dr Jeffery Hii	Topical repellents don't cost a lot of money. A 50 ml tube of OFF repellent lotion cost $0.80 which works out to be $0.027 per person per day or $4.80 per person per year at an application rate of 4 hours per day. A 50 ml-tube can provide approx. 20 applications. The bigger question is around whether topical repellent is good value for money in comparison to other options.
Dr Indra Vythilingam	Most of these forest goers are not rich people and thus should be provided with the repellents. Will they use is another question
Dr Rupam Tripura	

Question	**To Dr Rupam Tripura:** What is the AL resistance status in your study site, Dr Rupam? Did you also assess before and after drug resistance situation among study participants? If yes, please let me know the changing (or not) resistance situation? *From Win Han Oo*
Dr Rupam Tripura	One trial so far I can find in a small number of patients that was conducted during 2002-2003 in western Cambodia related to artemether-lumefantrine efficacy: Mey Bouth Denis et al. (Trop Med Int Health. 2006 Dec;11 (12):1800-7.). PCR corrected the cure rate was 71.1% in study AL2002 without fatty food, 86.5% in study AL2003 with fatty food. Author stated that further investigations were necessary to determine whether resistance of Plasmodium falciparum isolates to lumefantrine is present in the region.

	Most recently (2018-2019), we conducted a trial in Cambodia where triple Artemisinin based therapy (AL+AQ) vs ACT (AL) both in western and north-eastern Cambodia with a reasonable sample size, which will answer definitely whether AL works in Cambodia as the patients were monitored drug intake at hospital and followed up closely until day 42 But the rationale to use the drug AL for the ongoing prophylaxis trail: • AL is very safe and used by millions. • AL is not first line treatment in Cambodia and no resistant reported at study site target areas. • Low transmission setting • We are not treating clinical cases; these are healthy indivisuals, a proportion who might have very low-density parasite, which will be cleared by first 3 days full therapeutic dose before starting the weekly prophylactic dose. (R Tripura et al. Clinical Infectious Diseases 67(6) · March 2018 DOI: 10.1093/cid/ciy196)

Question	Interested in prophylaxis but compliance again a big issue which might increase the drug resistance as it is already a big problem in our region. *From Tobgyel Tobgyel*
Dr Rupam Tripura	Actually, compliance will not be a big issue. According to our unpublished data, people are aware that they may get malaria when they go to forest Around 80% of them buy medicines particularly for fever from private clinics and carry hammock nets with them. In our case, only one participant did not want to continue after 28 days so far. The main issue is the drug choice. The drug has to be well tolerated.

Question	To Dr Jeffery Hii: **As commented by Dr Leo, use of Insecticide treated Bands can be an option for Forest workers. Do you think there is room for such an intervention? Getting a WHO PQ for this would be tough, how should we proceed in such cases?**
Dr Jeffery Hii	There are toxicity risks of treated bands so need to determine dermal absorption NOEL and risks versus benefits analysis. A small number of wrist bands, bracelets and patches are registered in USA, Europe, Australia as mosquito repellents. These are infused with botanical products such as citronella or peppermint oil. The vapour released purportedly keeps mosquitoes away. Wrist bands containing botanical products provide very little protection. While topical formulations containing plant extracts may repel some mosquitoes, the vapours released from these wrist bands just aren't strong enough to block mosquito bites. One detailed study using wrist bands infused with botanical extracts found there was a reduction in biting mosquitoes, but only for a few cm either side of the band (Webb G & Russell RC. Do wrist bands impregnated with botanical repellents assist in repelling mosquitoes? Gen. Appl. Ent 2011; 40: 1-5. Wearing a wrist band won't provide "whole body" protection. Laboratory studies have shown that wrist bands impregnated with DEET provide some protection against mosquitoes (Jensen T et al. Field efficacy of commercial antimosquito products in Illinois. JAMCA 2000; 16: 148-152). But a key selling point of

	wrist bands and patches containing botanical extracts is that they're an alternative to DEET. They're primarily marketed to those looking for a "natural" alternative.
Dr Indra Vythilingam	Perhaps we should consider DEET impregnated head band and wrist bands

Question	To Dr Rupam Tripura: Do you take blood samples or DBS of any of the participants should they become malaria positive (to identify the Plasmodium spp.)? As you have GPS data it would be great to correlate species with location. *From Andrea Ruecker*
Dr Rupam Tripura	Yes, we will collect DBS from participant if they get malaria while taking drug for prophylaxis. We will also collect GPS data and link with malaria cases GPS data

Question	To Dr Rupam: Thank you Dr for your presentation. For those health workers that need to go to forest frequently (eg: monthly) for vector monitoring or research studies, do you recommend the prophylaxis? I am just concern on the possible accumulating side effects in long terms. Any recommendations? *From Nantha Kumar Jeyaprakasam*
Dr Rupam Tripura	Definitely, I think It will be beneficial for those who are exposed to high-risk areas. From our trial, we will find out if AL is effective and does not have any accumulating effect.

Question	To Dr Rupam: Very effective presentation Dr. Rupam. You mentioned that recruitment of females was challenging and on the other hand u said that significant female population 25% was willing to visit forests. Seems to be contradictory *From Neera Kapoor*
Dr Rupam Tripura	So far, 25 % of females were visiting forest but recruitment was challenging because we had to exclude around 65 % of them from trial because they could not comply with protocol e.g. either pregnant or plan to become pregnant.

Question	A forest worker equals someone going to cut it down, often illegally. is the problem not political? *From Jacques Charlwood*
Dr Bill Hawley	I had the same problem in Mondolkiri. seems like the great majority of overnight states are loggers.
Dr Jeffery Hii	Of course there are politics involved in illegal logging as local politicians are often involved in this business. In Attapeu province, I was cautioned not to get too close to logging campsites as there are security risks. This issue requires high level of ministerial intervention.
Dr Rupam Tripura	Of course, it is a very sensitive matter deal with forest workers. That is why it is so important to have Village Malaria Workers involved and play central role for any intervention related to forest work.

Question	To Dr Jeffrey Hill: what kind of lotions/aerosols as repellent would be good and available in India?

	From Ipsita Pal bhowmick
Dr Jeffery Hii	Two repellents – DEET (diethyltoluamide), IR 3535 ((3- [N-butyl-N-acetyl], aminopropionic acid ethyl-ester) or KBR3023 (also called Icaridin or Picaridin) are approved by WHO (in areas with potential transmission of Zika virus and other diseases transmitted by Aedes and other day-biting mosquitoes). https://www.who.int/csr/disease/zika/information-for-travelers/en/. Advanced Odomos cream developed by M/s. Balsara Home Products Ltd. (now M/s. Dabur Research Foundation, Sahibabad, UP) was evaluated for its efficacy under lab and field conditions against Anopheles and Aedes mosquitoes. Complete (100%) protection was achieved at 10 mg/cm 2 cream formulation of Advanced Odomos (1.2 mg a.i/cm 2) dose against An. stephensi and 12 mg/cm 2 (1.44 mg a.i./cm 2) against Ae. aegypti on human baits. There was no statistically significant differences in per cent protection against mosquito bites between Advanced Odomos and DEET cream (P>0.05) in respective doses. Complete protection up to 11 h was observed against Anopheles mosquitoes during whole night collections and up to 6 h against Ae. aegypti in day time collections. No adverse reactions such as itching, irritation, vomiting, nausea, etc. were reported by the volunteers. Advanced Odomos cream applied at 10 mg/cm 2 concentration provided 100% protection from Anopheles mosquitoes up to 11 h whereas about 6 h protection was recorded against Ae. aegypti. The laboratory and field trials indicate that for longer protection against Anopheles mosquitoes 10 mg/cm 2 will be appropriate and in case of Ae. aegypti more than 10 mg/cm 2 application is required for complete protection. In conclusion, the Advanced Odomos cream was comparable to the known repellent cream DEET for prolonged protection against malaria and dengue vectors [Mittal P et al Effcacy of Advanced Odomos repellent cream (N, N-diethyl-benzamide) against mosquito vectors. The Indian J Med Res 2011; 133: 426-3.

Question	To Dr Rupam: For the implementation of chemoprophylaxis excluding pregnant women or women likely to become pregnant will miss it seems a considerable number of forest goers. How about children under 18 as well? *From Prudence Hamade*
Dr Rupam Tripura	Yes, Implementation of chemoprophylaxis with exclusion of pregnant women or those who likely to become pregnant will miss a considerable number of forest goers. This can be minimize through adequate explanation and encouraging couples to use contraceptive method e.g. in our case use of condoms as AL decreases the effectiveness of hormonal method. Definitely, children below 18 years can join. This is one of the recommendations from participants during community meetings. We have a plan to add participants below 18 years after consultation with National Center for Parasitology, Entomology and Malaria Control, Cambodia.

Question	My question was on LSM cost effectiveness *From Pradeep Srivastava*
Dr Bill Hawley	
Dr Jeffery Hii	See above

Dr Indra Vythilingam	
Dr Rupam Tripura	

Question	**To All speakers:** Are the challenges of insecticide resistance in APMEN area different from those in Africa: is there a difference in priorities for further insecticide development due to the spectrum of resistance types? *From Ian Boulton*
Dr Bill Hawley	Insecticide resistance is not as well documented as in Africa, but seems more spotty and less intense than in, certainly, West Africa. There are greater challenges in Asia, due to the larger variety of vectors and difficulty in separating the species complexes, whereas in Africa we can focus on gambiae, coluzzii, and funestus for the most part

Question	The biggest impact of Covid is on our Community volunteers who are scared to test Fever cases. **Under GF RAI-3E initiative we are aiming to eliminate Pf in all the GMS countries by 2023** *From Faisal Mansoor*
Dr Bill Hawley	Hi Faisal, yes, the GF procurement is tied to WHO recommendations. Thus, government funding might be used instead.
Dr Jeffery Hii	You are right, Unless WHO gives a go ahead, we cannot buy repellents with GF funding

Comment	Unfortunately, repellent trial was good while being supervised once that has gone compliance falls off the cliff. *From john Invest - Sumitomo UK*

Comment	As Dr Hii mentioned, we found efficacy of repellent delivered by village health volunteers on malaria incidence, but falciparum only. *From Julia Cutts*

Question	Jeffrey is quite correct and the required two epi trials can cost c$3 million!! This is a huge barrier to innovation. *From John Invest - Sumitomo UK*
Dr Bill Hawley	
Dr Jeffery Hii	For proven malaria and arbovirus interventions (e.g. SIT/IIT approach), "VCAG recommends that duration of epidemiological assessment, excluding the baseline period, should cover at least two years, to account for inter-annual variation in transmission" (8th VCAG meeting report. Geneva: WHO; 2018; https://apps.who.int/iris/bitstream/handle/10665/273106/WHO-CDS-VCAG-2018.01-eng.pdf. The minimum requirement for WHO to initiate the process of evidence review and policy formulation is two epidemiological trials. The minimum number of "two" is based on the need for at least some degree of replication of results from different studies as a precondition for any assurance that an intervention will be generalizable. More trials with epidemiological endpoints may, however, be required if the initial two studies generate contradictory results or suffer from design limitations that precluded comprehensive assessment of potential epidemiological impact. 10th VCAG meeting report. Geneva: WHO; 2019;

	https://apps.who.int/iris/bitstream/handle/10665/326584/WHO-CDS-VCAG-2019.02-eng.pdf?ua=1

Comment	A response to the questions about use of repellents, the WHO Guidelines for Malaria Vector Control show limited evidence from RCT for effectiveness: “Despite the potential to provide individual protection against bites from malaria vectors, the deployment of the above personal protective methods in large-scale public health campaigns has been limited, at least partially due to the scarcity of evidence of their public health value. Daily compliance and appropriate use of the repellents seem to be major obstacles to achieving such potential impact (38). Individuals’ use of the intervention to achieve personal protection faces the same obstacles.”" *From Tom Burkot*

Question	Has there been any evidence of simian malaria in Africa? *From Prudence Hamade*
Dr Jeffery Hii	Recent studies on great apes in Africa have revealed the existence of a large diversity of Plasmodium parasites infecting chimpanzees and gorillas, some being related to the most deadly human parasite Plasmodium falciparum (subgenus Laverania), others to the human parasites Plasmodium malariae, Plasmodium ovale, or Plasmodium vivax [Duval L et al African apes as reservoirs of Plasmodium falciparum and the origin and diversification of the Laverania subgenus. Proc Natl Acad Sci USA 107(23):10561–10566].
Dr Indra Vythilingam	There was a report of a Ape type P. vivax in a traveler from Europe. But apart from that, there is little evidence. No Ape Laverania in humans for example

Question	To Dr Indra: Reservoir of P.k are monkeys and how about reservoir of Pf and pv in the forest? *From Chinh*
Dr Jeffery Hii	Asymptomatic naturally acquired P. cynomolgi and P. knowlesi infections can both occur in humans. “They were detected in 1361 of 14732 samples (9.2%). Asymptomatic infections with nonhuman primate malaria parasites were found in 21 individuals living close to forested areas; P. cynomolgi was found in 11, P. knowlesi was found in 8, and P. vivax and P. cynomolgi were both found in 2. Only 2 subjects were female, and 14 were men aged 20–40 years. Geometric mean parasite densities were 3604 parasites/mL in P. cynomolgi infections and 52488 parasites/mL in P. knowlesi infections. All P. cynomolgi isolates had wild-type dihydrofolate reductase genes, in contrast to the very high prevalence of mutations in the human malaria parasites. Asymptomatic reappearance of P. cynomolgi occurred in 2 subjects 3 months after the first infection.” JID 2019; 219: 695–702, https://doi.org/10.1093/infdis/jiy519
Dr Indra Vythilingam	As for Pf and Pv it must be the humans who are infected and are there perhaps asymptomatic

Question	To Dr Indra: *How do you propose to control the pathogen from asymptomatic persons?* *From Dipsikha Bora*
Dr Jeffery Hii	Asymptomatic infections can act as precursors to malaria illness (34). MDA has been suggested as an effective way of treating chronic asymptomatic infections (Newby et al Am J Trop Med Hyg. (2015) 93:125–34; Sturrock HJW et al PLoS Med. (2013) 10:e1001467). However, this may interfere with the immunity maintained by these infections, thus increasing the risk of developing clinical malaria in asymptomatic individuals (Smith TA et al Trans R Soc Trop Med Hyg. (1999) 93 (Suppl. 1):59–64). A study in Mali treated chronic asymptomatic individuals at the end of the dry season, followed them up during the subsequent rainy season and reported that treatment of asymptomatic infections is unlikely to influence the subsequent risk of developing clinical malaria (Portugal S. et al. Clin Infect Dis. (2017) 64:645–53). Similar findings were also reported in Burkina Faso (Tiono AB et al Malar J. (2013) 12:79). A risk-benefit analysis is required to determine the tradeoffs to inform the public health impact of MDA on asymptomatic infections. The possibility of developing febrile malaria among asymptomatic carriers has been shown to vary due to transmission intensity and age (Njama-Meya D et al Trop Med Int Heal. (2004) 9:862–8; Wamae K et al J Infect Dis. (2018) 219:936).
Dr Indra Vythilingam	This is a big problem. That is why we need to screen with molecular tools

APMEN would like to thank all of our panelists for their time and sharing their knowledge.

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