Meeting Report

3rd Meeting of the Pacific Malaria Drug Resistance Monitoring Network

16–17 June 2014
Manila, Philippines
REPORT

3rd MEETING OF THE PACIFIC MALARIA DRUG RESISTANCE MONITORING NETWORK

Convened by:
WORLD HEALTH ORGANIZATION
Western Pacific Region

Manila, Philippines
16–17 June 2014
NOTE

The views expressed in this report are those of the participants in the Pacific Malaria Drug Resistance Monitoring Network Meeting and do not necessarily reflect the policies of the World Health Organization.

Key words: malaria, drug resistance, therapeutic efficacy studies, Pacific, regional network

This report has been printed by the World Health Organization Western Pacific Region for governments of Member States in the Region and for those who participated in the Pacific Malaria Drug Resistance Monitoring Network Meeting, held in Manila, Philippines from 16–17 June 2014.
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Keywords:
Drug resistance / Malaria - drug therapy / Drug monitoring / Antimalarials / Sentinel surveillance / Pacific Islands
<table>
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ACPR</td>
<td>Adequate Clinical and Parasitological Response</td>
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<td>ACT</td>
<td>Artemisinin-based Combination Therapy</td>
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<td>ADB</td>
<td>Asian Development Bank</td>
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<td>AL</td>
<td>Artemether-Lumefantrine</td>
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<td>AMI</td>
<td>Australian Military Institute</td>
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<td>AMO</td>
<td>Amodiaquine</td>
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<td>API</td>
<td>Annual Parasite Incidence</td>
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<td>APMEN</td>
<td>Asia Pacific Malaria Elimination Network</td>
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<td>AusAID</td>
<td>Australian Agency for International Development</td>
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<tr>
<td>CQ</td>
<td>Chloroquine</td>
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<tr>
<td>DHA</td>
<td>Dihydroartemisinin</td>
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<tr>
<td>DHP/DHA-PPQ</td>
<td>Dihydroartemisinin-Piperaquine</td>
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<tr>
<td>DOH</td>
<td>Department of Health</td>
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<tr>
<td>ECA</td>
<td>External Competency Assessment</td>
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<td>ERAR</td>
<td>Emergency Response to Artemisinin Resistance</td>
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<td>G6PD</td>
<td>Glucose-6-Phosphate Dehydrogenase</td>
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<td>GFATM</td>
<td>The Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<td>GMP</td>
<td>Global Malaria Programme</td>
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<td>GPARC</td>
<td>Global Plan for Artemisinin-Resistance Containment</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>K13</td>
<td>Kelch 13 mutation</td>
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<td>MOH</td>
<td>Ministry of Health</td>
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<td>MVP</td>
<td>Malaria and other vector borne and parasitic disease unit</td>
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<td>NMCP</td>
<td>National Malaria Control Program</td>
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<tr>
<td>Pf</td>
<td><em>Plasmodium falciparum</em></td>
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<td>Pk</td>
<td><em>Plasmodium knowlesi</em></td>
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<tr>
<td>Pm</td>
<td><em>Plasmodium malariae</em></td>
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<tr>
<td>Pv</td>
<td><em>Plasmodium vivax</em></td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PQ</td>
<td>Primaquine</td>
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<td>QA</td>
<td>quality assurance</td>
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<td>RBM</td>
<td>Roll Back Malaria</td>
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<td>RDT</td>
<td>rapid diagnostic test</td>
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<td>RITM</td>
<td>Research Institute for Tropical Medicine</td>
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<td>SOP</td>
<td>standard operating procedure</td>
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<td>SP</td>
<td>Sulfadoxine-Pyrimethamine</td>
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<td>TEG</td>
<td>Technical Expert Group</td>
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<td>TES</td>
<td>therapeutic efficacy studies</td>
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<tr>
<td>WEHI</td>
<td>Walter and Eliza Hall Institute of Medical Research</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SUMMARY

The emergence and spread of malaria drug resistance is a major public health problem. The spread of artemisinin-resistant falciparum-malaria in the Greater Mekong Subregion is of particular concern, putting achievements to date at risk. Country efforts to track malaria drug resistance through implementation of high-quality therapeutic efficacy studies (TES) need to be supported and information shared in a timely manner across all malaria-endemic countries, to prevent the spread of drug resistance.

As part of this effort, WHO and Member States in 2011 established the Pacific Malaria Drug Resistance Monitoring Network. Operating in parallel to the Greater Mekong Subregion Network, the Pacific Network covers Malaysia, Papua New Guinea, Philippines, Solomon Islands and Vanuatu in the Western Pacific Region and Indonesia and Timor-Leste in the South East Asia Region.

Now in its fourth year, the Pacific Network held its third meeting in Manila, Philippines, from 16 to 17 May 2014. The meeting was attended by country representatives from five of the seven member countries: Indonesia, Malaysia, Philippines, Solomon Islands and Vanuatu. Two temporary advisers, two observers, and eight WHO Secretariat staff also attended.

The objectives of the meeting were: 1) to assess antimalarial drug efficacy data generated in countries and existing monitoring systems, the appropriateness of current national malaria treatment policies based on data presented, and to identify key issues and gaps; 2) to review and update country plans for antimalarial drug efficacy monitoring for the next two years; and 3) to discuss and further develop the Pacific Malaria Drug Resistance Monitoring Network plan of action, including partner cooperation, resource mobilization and linkages with other networks.

The meeting included country updates, technical presentations, and group and plenary discussions. The country representatives shared the status of malaria, treatment policy and latest TES results, highlighting the absence of resistance to artemisinin-based combination therapy (ACTs) in participating countries. They also reviewed their 2013–2014 malaria drug efficacy monitoring plans and identified accomplishments as well as gaps and operational issues and bottlenecks. These discussions subsequently informed the development of the new 2014–2015 country plans. Common challenges identified included difficulty reaching the minimum required sample size in view of the decline in malaria burden in many areas, problems identifying sentinel sites, lack of local institutions to conduct the TES, shortage of laboratory support for molecular analysis, and human resource issues. The importance of quality assurance for malaria microscopy was highlighted in therapeutic efficacy monitoring.

Country TES plans for 2014–2015 were developed in country groups. Planned activities include continuation of ongoing TES, ensuring the use of the updated TES template from WHO, setting-up or strengthening of quality assurance systems for microscopy, and commencement of new TES in alternative sites where necessary. Funding for TES activities in most countries will come from national malaria programme budgets, while some will need funding support. Among the seven countries of the network, not all countries had been able to carry out TES as planned and according to WHO protocol. A strong role of the network was highlighted in capacity-building, supporting TES implementation, quality control and coordination, information sharing and dissemination, and inter-country exchange and collaboration.

A newly identified molecular marker for artemisinin resistance, known as K13, was discussed. The network will help to coordinate and implement use of this marker in collaboration with technical partners, and funding will be available from the network for this work. A number of technical questions on the use and interpretation of the K13 marker need clarification. This will be discussed at a WHO technical meeting in Geneva in September 2014. Further guidance will be provided through the network.
Recommendations

All seven network countries should carry out high-quality TES of their national first-line malaria treatment regimens for \( Pf, Pv \) (and \( Pk \) in Malaysia) in 2014–2015 in line with agreed work plans and following WHO standard TES protocol. The network should support countries in TES planning efforts and implementation as required. Areas of support highlighted by countries included:

1. Building capacity, including through intercountry exchanges, involving regional training in TES preparation and implementation targeting principal investigators, national TES teams and microscopists; organizing "writeshops" to prepare TES routine reports and publish manuscripts.
2. TES implementation support, including provision of quality-controlled drugs, topping up country TES budgets if needed, sharing of SOPs (e.g. for blood filter paper collection for genotyping and K13 testing, data entry/management), sharing reporting templates and checklists, and support in data analysis.
3. Coordinating laboratory support for parasite molecular work.
4. Supporting quality assurance of TES, including provision of clinical monitors (including establishment of a roster of qualified national monitors from network countries to assist monitoring in other countries).
5. Support quality microscopy in all countries, through external competency assessment (ECA), including for microscopists based in research institutions involved in TES and clinical trials, to develop a pool of qualified TES microscopists, foster sharing of microscopy expertise among countries, e.g. for validation of TES slides.

It was further recommended that the network support information sharing between countries, including assistance to publish results (e.g. through technical reviews). The network should seek to mobilize partners and resources and maintain close links with the Greater Mekong Subregion TES Network.

The network should encourage and support implementation research to explore new ways of selecting TES sentinel sites, ways to include private health facilities in TES implementation, and implementation of national malaria treatment guidelines. Other operational research topics include antimalarial drug quality and availability surveys in public and private health facilities.
1. INTRODUCTION

The growing threat of resistance to artemisinin has become a global concern. Networks in the Greater Mekong Subregion and in the Pacific have been established to intensify drug efficacy monitoring and collect evidence on the status of drug resistance in countries across these regions. The Pacific Malaria Drug Resistance Monitoring Network was established in 2011 to strengthen the capacity of the region to prevent and address artemisinin resistance, coordinate therapeutic efficacy monitoring and inform programme decisions. The 3rd Pacific Network Meeting served as the venue for following-up on the recommendations presented during the 2nd Pacific Network Meeting. This meeting aimed to review Pacific data on antimalarial drug resistance and discuss implications for national treatment guidelines, and jointly plan the way forward for countries and the Network. The 3rd Meeting brought together national malaria programme managers and focal persons on malaria drug resistance surveillance from five countries: Indonesia, the Philippines, Malaysia, Solomon Islands and Vanuatu. It also brought together other stakeholders, partners and technical experts to collaborate and define the way forward. The WHO Regional Office for the Western Pacific, in collaboration with the WHO Regional Office for South-East Asia, and its partners, organized the meeting. The meeting took place from 16 to 17 May 2014 in Manila, Philippines. The programme and list of participants are available at Annexes 1 and 2 respectively.

1.1 Objectives

1) to assess antimalarial drug efficacy data generated in countries and existing monitoring systems, the appropriateness of current national malaria treatment policies based on data presented, and identify key issues and gaps;
2) to review and update country plans for antimalarial drug efficacy monitoring for the next two years; and
3) to discuss and further develop the Pacific Malaria Drug Resistance Monitoring Network plan of action, including partner cooperation, resource mobilization and linkages with other networks.

1.2 Opening remarks

Dr Eva Maria Christophel welcomed all the participants and remarked that while encouraging progress has been made in the South-East Asia and Western Pacific regions, worsening drug resistance is a threat that needs to be tackled with urgency. She outlined the meeting agenda which included discussion on drug resistance data collection in the Pacific and how to strengthen collection of quality data within the next two years. Availability of sufficient quality data will mean the actual status is known and appropriate action can be taken accordingly. She encouraged the participants to make maximum use of the opportunity to share experiences and interact with experts in the field.

Dr Mark Jacobs, Director, Combating Communicable Diseases of the WHO-WPRO, delivered the opening remarks on behalf of WHO Regional Director for Western Pacific Region Dr Shin Young-soo. He emphasized that the growing resistance to artemisinin and other antimalarial drugs has become a global concern and the urgency for countries to contain further spread. Underlying factors must be addressed such as weak health systems, the need for regular monitoring drug efficacy in countries and the lack of review of drug guidelines.

Dr Jacobs recounted the expansion of artemisinin resistance in the Greater Mekong Subregion which prompted the development of the Emergency Response to Artemisinin Resistance (ERAR) which has among its priority activities the involvement of non-health sector such as mobile populations. He acknowledged the support from funding partners such as the Bill and Melinda Gates Foundation,
USAID, the Australian Government Department of Foreign Affairs and Trade (DFAT) and the Global Fund to Fight AIDS, Tuberculosis and Malaria.

Dr Jacobs pointed out that currently, the network’s issue is not one of funding, but of high quality implementation. Good planning, high quality and reliable monitoring and evaluation are needed, along with critical analysis and the urgency of early detection to be followed by swift response.

1.3 Nomination of Chair, Vice Chair and Rapporteur

Dr Mark Jacobs called for the nomination of chairperson, vice-chairperson and rapporteur. Mr Albino Bobogare, Director, National Vector Borne Disease Control Programme, Ministry of Health and Medical Services in Solomon Islands was nominated as chairperson. Dr Din Syadrudin, Senior Research Fellow and Head of Malaria and Pathogen Resistance Laboratory, Eijkman Institute for Molecular Biology in Indonesia was nominated as vice-chair. Dr Fe Esperanza Espino, Head, Department of Parasitology and National Reference Laboratory for Malaria and Other Parasites, Research Institute for Tropical Medicine in the Philippines, was nominated as rapporteur.

2. PROCEEDINGS

2.1 Technical session 1: update on tracking and mapping of antimalarial drug efficacy and drug resistance globally and in the Western Pacific Region

Dr Lasse Vestergaard presented global updates on tracking and mapping antimalarial drug efficacy. Therapeutic efficacy studies (TES) provide evidence for updating treatment guidelines which is important because of the inevitable eventual failure of all antimalarial drugs. The network’s role is to step up evidence gathering in support of updating national malaria treatment policies.

The WHO standard protocol for TES is the “gold standard” for monitoring drug efficacy and for updating malaria treatment policies. The current protocol version is from 2009. It is largely adopted by all countries and most research institutes and is designed for all antimalarials, including artemisinin combination therapy (ACTs). It is routinely used for testing of first and second line antimalarial drugs and used for both P falciparum and P vivax.1

The requirements for generating quality TES data include: 1) following standardized protocols, 2) using standard case record forms and consent forms, 3) ethical clearance, 4) use of quality assured drugs, 5) use of quality assured diagnostics such as standard malaria microscopy with slide validation and standard PCR techniques for parasite genotyping, 6) quality data management and 7) regular monitoring/field supervision.

Other TES-related WHO publications include the In Vitro drug resistance manual, malaria microscopy quality assurance manual and the genotyping manual which are available for all member countries.

Therapeutic efficacy test outcomes are based on clinical and parasitological outcomes detected during patient follow-up. Adequate clinical and parasitological response (ACPR) at more than 90% is the agreed threshold. If it drops below 90%, countries need to consider change in drug policy.

The various features of the WHO global antimalarial drug resistance database were presented. Majority of the data comes from published data found in scientific literature, followed by unpublished reports, with raw data as the least common source. The presenter highlighted that many countries would often have unpublished data available on record, which is critical to share to ensure timely and accurate updates of the drug resistance database.

Majority of data are on *P. falciparum*. In terms of WHO regions, studies on *P. falciparum* done from 2005 to 2013 are mostly from the African, South-East Asia and Western Pacific regions. Studies which followed the WHO protocol are included in the database, for comparability. In the Western Pacific Region, majority of the studies are on ACTs such as Artesunate+Mefloquine (AS+MQ). Cambodia has the most studies included in the database, followed by Philippines and the Lao People's Democratic Republic. Studies are not done routinely across the Region and there is a need for this to be a more regular activity.

Online reporting includes the global report, summary tables and maps. The global report on antimalarial drug efficacy and drug resistance is a summary report of studies done per country and according to results, a way of tracking the status of drug resistance in each country.

There are various ways the encoded data can be presented e.g. by country or by results. The Western Pacific Region *Pf* TES sites on maps (Figure 1) which currently has data on 152 sites across the world was shown. Maps can be customized by treatment, study outcome indicator, geographic area, and year.

![Figure 1. Antimalarial drug efficacy TES sites (for Pf) including in the Western Pacific Region](image)

Updates on the Pacific Malaria Drug Resistance Monitoring Network, which has had two meetings since 2011, were presented.

The recommendations from the 2013 network meeting focused on ensuring the full and quality implementation of TES country plans following the WHO standard protocol. Areas of support by the Network are capacity building, strengthening of existing partnerships, exchange of data and information, independent monitoring of TES, quality assurance of microscopy and data validation. The focus of this year’s meeting is directed on the practical aspects of how to do TES in the field.

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2.2 Technical session 2: South East Asia Region updates on malaria situation and drug efficacy monitoring

Dr Maria Dorina Bustos updated on the malaria situation and drug efficacy in the South East Asia Region. There is an estimated 1.4 billion people are at risk in the Region across 10 malaria-endemic countries. As of 2012, there were 2 million estimated malaria cases and 1200 malaria deaths. Around 96% of reported malaria cases and deaths are from India, Indonesia and Myanmar.

From 2000 to 2012 reported cases have decreased from 2.9 million to 2 million and deaths from 6500 to 1200. Five countries have achieved more than 75% decrease in case incidence and two countries are projected to achieve more than 75% decline by 2015. Sri Lanka is in elimination phase while Bhutan and the Democratic People's Republic of Korea are in pre-elimination phase. Maldives has been malaria free since 1984 and is currently being assessed for certification.

District-wide distribution of annual parasite incidence (API) in the Region as of 2010 shows very focal distribution in border areas, with a heavy load in the Indonesian Papua Island. There is decreasing trend in cases and deaths, API, mortality rate and case fatality rate in the past decade. Distribution of ACTs and reported deaths in the South-East Asia Region 2004–2011 shows that with increasing access to ACTs, there is declining mortality trend in the Region (particularly from 2009 onwards).

For country updates, Bangladesh data showed the emergence of drug resistance to different antimalarials. Over the years, there was growing resistance of *P. falciparum* to Chloroquine, and later to combination Chloroquine + Sulfadoxine-pyrimethamine (SP), as well as to oral quinine plus SP combination and to mefloquine. With encouraging TES results of artemether-lumefantrine (AL), the programme shifted from Chloroquine to AL in 2004, with the wide-scale implementation beginning in 2007. Ongoing study shows 100% ACPR to AL.

In Bhutan, studies started in 2006 testing the efficacy of ACT against *P. falciparum* and CQ-PQ against *P. vivax*, have shown 100% ACPR.

In India, efficacy study sites were set up to test ACT (*Pf*) and CQ (*Pv*) from 2009 to 2012. At present, AS+SP is well tolerated and highly effective for *P. falciparum* malaria, except in northeast India. Chloroquine remains effective in *P. vivax* malaria with 100% cure rates. The nationwide sentinel site system, with >40 sentinel sites strategically located from 2010 to present, was established to monitor antimalarial drug resistance involving high quality data, longitudinal trend, national representation, coordinated use of resources and pooled data analysis.

API is declining in Indonesia from 4.68 in 1990 to 1.37 in 2013. *Pf* parasite clearance to ACTs remains fast at less than 48 hours, but there is a need to further strengthen surveillance and efficacy monitoring. In North Papua, mefloquine, and halofantrine and atovaquone-proguanil were more effective than Chloroquine against *P. falciparum* and *P. vivax* infection and were used before the introduction of ACTs. ACTs are now used nationwide, in line with the Indonesia's treatment guidelines.

Monitoring of therapeutic efficacy of Artemether-Lumefantrine to treat uncomplicated *P falciparum* malaria in districts of Nepal, from 2008 to 2011, showed adequate clinical and parasitological response.

In Sri Lanka, the decreasing number of cases has made it difficult to get enough samples. The programme instead conducts case surveillance through a 28-day hospital-based study for each confirmed case. So far, only imported cases have been reported.
The efficacy of some antimalarial drugs can be reduced in pregnant women and infants. Pregnancy affects metabolism and volume distribution of drugs; while in infants, there is slower drug absorption, faster elimination and lower plasma drug concentration. The evolution of Pf resistance to artemisinin in the Greater Mekong Subregion which first emerged in western Cambodia after 30 years of deployment was presented. The tier map of Artemisinin Resistance in the Subregion (Figure 2) is regularly updated, with the following definition of the tiers: 1) Tier 1 – areas with credible evidence of artemisinin resistance, 2) Tier 2 – areas with significant inflows of mobile and migrant populations from Tier 1 areas or shared borders with Tier 1 areas, and 3) Tier 3 – Pf endemic areas with no evidence of artemisinin resistance and limited contact with Tier 1 areas.

![Figure 2. Artemisinin resistance in the Greater Mekong Subregion tier map (Updated 23 January 2014)](image)

The map in Figure 2 shows areas of suspected resistance to artemisinins (where more than 10% of enrolled patients still have parasites 72 hours after start of treatment). Data from 2008 to 2012 was presented, with focus on southwestern Yunnan province in China, southwestern Viet Nam, western Cambodia, western and southeastern Thailand, and eastern Myanmar. In 2012, with the use of Kelch 13 markers for artemisinin resistance, new areas of confirmed resistance were identified such as Champassak in the Lao People's Democratic Republic.

The TES sentinel sites of the Greater Mekong Subregion Network have been expanded to new sites since 2013, with sites in Bangladesh and northeastern India to monitor emergence or possible spread of resistance from the Subregion.

Since the 1950s, CQ and SP were the antimalarial drugs of choice in the South-East Asia Region but through time, efficacy has fallen rapidly for both Pf and Pv. These drugs are no longer recommended. The WHO recommendation is the use of ACTs with a ban on artemisinin monotherapy.

Significant progress has been achieved in the Subregion. Remaining challenges include the need for political and global cooperation, sustained financing, scaling-up access to interventions to reach the unreached, strengthening of surveillance, monitoring and evaluation and responsiveness.

The discussion that followed clarified that all countries in the Greater Mekong Subregion have been using the WHO protocol in the last three years. Day 3 monitoring of parasite clearance is also being
done but not the 6-hours parasite clearance half-life monitoring. Efficacy of the partner drug is monitored through the 28-day and 42-day follow-up. Participants suggested that a complementary tool such as in-vitro study may be used also. For monitoring monotherapy, WHO headquarters is tracking companies that produce monotherapy drugs or those that they have already banned.

2.3 Technical session 3: update on the emergency response to artemisinin resistance in the Greater Mekong Subregion

Dr Eva Christophel updated on the Emergency Response to Artemisinin Resistance (ERAR) in the Greater Mekong Subregion on behalf of Dr Walter M. Kazadi, ERAR Hub Coordinator. Artemisinin resistance was first reported from eastern Cambodia and has now spread to five countries in Greater Mekong Subregion, namely the Lao People's Democratic Republic, Myanmar, Thailand (Thailand-Cambodia border), Cambodia and Viet Nam. The ERAR project aims to accelerate the elimination of *P. falciparum* malaria where possible and in areas where elimination is not possible, to rapidly lower the burden. The Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Subregion assessed that the approach was appropriate and a good start, but concluded that there is a need to step up the intensity, coverage and quality of the response.

WHO subsequently developed the *Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: A regional framework for action 2013–2015*. The framework proposes 15 priority actions focused on four areas: 1) full coverage of quality interventions in priority areas including working with health and non-health sectors to reach high-risk populations, 2) tighter coordination and management of field operations including increasing monitoring of staff performance and supportive supervision, 3) better information for resistance containment including fast tracking priority research and refining tools for containment and elimination, and support to translate evidence into policy and practice, and 4) strengthening regional oversight and support including support to improve cross-border coordination.

The WHO ERAR Regional Hub (ERAR Project) is funded through agreements between WHO and Bill & Melinda Gates Foundation (US$ 11 million) and the Australian Government Department of Foreign Affairs and Trade (then AusAID) (US$ 4.5 million) for three years. The project goal is to strengthen regional response to artemisinin resistance by coordinating actions across countries, strengthening leadership and catalyzing resource mobilization. The objectives are:

1) Strengthen leadership, coordination and oversight mechanism;
2) Maintain and expand drug efficacy surveillance networks and accelerate priority research;
3) Improve access for migrant and mobile populations to quality services;
4) Facilitate the full implementation of the Myanmar Artemisinin Resistance Containment (MARC) framework;
5) Strengthen the response to artemisinin resistance in Viet Nam; and
6) Limit the availability of oral artemisinin-based monotherapy, substandard and counterfeit antimalarial medicine while improving quality of artemisinin-based combination therapies.

Artemisinin resistance is spreading and emerging independently. The Lao People's Democratic Republic has been included in Tier 1. The countries are also discussing whether to have the whole Mekong in Tier 2. Each tier has a package of interventions and should have a high level of interventions. A feasibility study is also being conducted on whether the whole of the Mekong Region should go for elimination – a move that will require substantial funding to be carried out.

In conclusion, ERAR is a much needed response to a growing threat to recent gains in malaria control/elimination. Research is a key part but needs to be coordinated so that information is available readily when needed. In the Pacific, there are risk factors for artemisinin resistance. Monitoring has to go beyond the Mekong to detect the problems early. The landscape is rapidly changing; hence there is need for continuous adaptation, better collaboration and strong coordination.
based on the ERAR framework. Gaps in knowledge and resources need to be addressed in a timely and coordinated way. Information generated is urgently needed to inform drug policy decisions and operational response at country level and in the Region.

2.4 Technical session 4: update on the new 2014 WHO TES template and use of the new excel data entry tool

Dr Dorina Bustos presented the new WHO TES template. The updates are based on recommendations from WHO headquarters Ethics Committee and experts involved in the development of the protocol template. She explained how each section should be filled out, citing new features of the template. The protocol covers investigational plan, treatment, evaluation, study assessment, data management, statistical methods, ethical considerations and budget template.

The criteria on site selection are in the protocol but the number of sentinel sites can vary across countries depending on the strategic location of the resistance. The country programme should complete the study with one drug first before proceeding to study the second drug. This will help avoid confusion in field implementation and facilitate systematic enrolment of patients for one drug and attainment of required sample size.

There is a new requirement to describe the transmission level in the study site and ensure access of the study population to the health facility conducting the TES. The Principal Investigator should explain the rationale for the selection of the target population and any exclusion based on age or gender. This is usually applied to those less than 2 years old and pregnant women and females of reproductive age who refuse to have a pregnancy test.

It is necessary to secure at all times the following: 1) informed consent from the patient or from a parent or guardian in the case of children aged less than (enter age of majority in this country) years; 2) informed assent from any minor participant aged more than 12 years and less than (enter age of majority in this country) years; and 3) consent for pregnancy testing from female of child-bearing potential and from their parent or guardian if under-aged.

Another inclusion criterion is mono-infection by microscopy. If PCR confirms a mixed infection, in principle, these patients should be excluded. This could be difficult, especially in situations where the proportion of mixed infections is 15% or higher. TES implementation in the field is based on microscopy-based diagnosis. Any PCR results will be considered in the final analysis and reporting.

For the laboratory, specifications for the microscopic blood examination were emphasized, including destruction of all filter papers immediately after completion of PCR analyses, unless informed consent was secured and the patient agreed that the samples may be used for studies other than the TES.

Other exclusion criteria emphasized include: severe malnutrition, weight under 5 kg, and inability or unwillingness to take a pregnancy test. Pregnancy detected during the course of follow-up does not constitute a reason for withdrawal, but the event must be recorded and managed accordingly, and the patient and newborn followed up after delivery.

For patient follow-up, details on house visit by health workers should be provided if this method is used. Implementing institutions should also decide when to destroy documents after completion of the analysis.

Data should be analysed by two methods: the Kaplan-Meier method and per-protocol analysis. Another new feature is the need to register the study on a public clinical trial registry.
The upgraded versions of the Excel data entry sheets were discussed. This includes the reference guide for data collection from antimalarial TES, study information (included in Maplink), drug information, patient information, summary at baseline and at follow-up, and the Kaplan-Meier analysis. The programme generates summary baseline patient characteristics and computes for the results at various points in follow-up. The template has features that screen the data for the study. For example, if the parasite count is too low, there is a warning sign for any "violations" in the protocol.

Discussion points included the importance of retaining filter papers for use in molecular markers determination, conducting pregnancy tests for under aged children and disclosure of test results to the parent or child or both depending on the decision of the local ethics committee, and following-up pregnant patients beyond 42 days (for the treatment outcome) up to completion of pregnancy. For countries that have difficulty obtaining samples because of low case numbers, one province can have different catchment areas. The half-life of drugs should be considered in determining the interval between initiation of arms, the inclusion criteria is a minimum parasitemia density of 500/ul for \( Pf \) and 250/ul for \( Pv \) (asexual forms). A microscopist who can do reliable counting is needed to ensure the accuracy of the parasite count and enrolment of the appropriate patients. The same template was proposed to be used for \( Pk \) with 28-day follow-up for AL. Exclusion of patients with mixed infections by PCR among samples that were initially diagnosed as mono-infection on microscopy. Data can be migrated from the old template to the new one. The group did not reach consensus on retaining documents, this will be determined by institutional ethical rules on duration of study document storage.

**Summary**

TES is important in updating national malaria treatment policy. There are various methods, manuals and tools available to help countries obtain quality data on the efficacy of antimalarial drugs and to conduct quality TES.

The malaria situation in the South-East Asia Region is improving with remarkable decline in malaria cases and deaths. TES is conducted in Bangladesh, Bhutan, India, Nepal, Sri Lanka (BBINS Network) and ACTs have been found to have generally good efficacy. Significant progress has been achieved but challenges remain in tracking drug resistance and determining efficacy in the Greater Mekong Subregion.

The ERAR is a response by WHO and global partners to the growing artemisinin resistance in the Subregion. It is critical for Pacific countries to systematically monitor and track efficacy of ACTs. The impact of the spread of artemisinin resistance will not be contained within the Region but will impact global health.

The updates on the TES protocol template and Excel data entry programme result from recommendations of the WHO Ethics Committee and other experts. They are intended to make the protocol and the template user-friendly and easier to navigate. All countries follow the standard WHO protocol and are eager to use the updated tools.

Discussion included that the additional inclusion criteria will affect meeting the required sample size. In Indonesia, a local advisory committee could provide guidance on subject selection (in view of the local situation), and other issues in the conduct of the study. Microscopy quality is important as TES depends on the results of the first reading of slides. The external competency assessment helps countries in the Pacific improve quality assurance of microscopy. Improving microscopy skills should be used for TES and there should be at least one level 1 microscopist in each country. Indonesia expressed the need for external quality assurance (EQA), hoping that within the network, expertise may be shared. The network's agenda should include setting up a system for sending slides to member countries to validate and use reference laboratory services. Malaysia offered support.
through training and use of slide banks to member countries. Quality assurance and validation of microscopy and data management should be built up prior to and within the study and not after. Site selection is also a challenge as case numbers decline. Suggestions include having a "feeder" health centre as in Indonesia where one health centre providing public health services sends patients to the sentinel site health facility. First-line drugs should be priority drugs for the TES. Countries should make sure that these work.

2.5 Technical session 5: country updates – malaria situation, treatment policy, drug resistance situation and monitoring, technical issues

2.5.1 Philippines

Dr Fe Esperanza Espino presented the update on behalf of the national programme. Malaria cases and deaths have been declining since 2005. Maps depicting the API trends from 1992 to 2006 in comparison with 2009 and 2012 (Figure 3) showed a gradual transition from high endemicity (red – colored areas) to low endemicity in the majority of the islands.

The Philippines treatment regimen for uncomplicated falciparum malaria consists of Artemether-Lumefantrine and Primaquine. For uncomplicated vivax malaria, Chloroquine and Primaquine are used. For mild to moderate G6PD deficiency, Primaquine 0.75 mg base/kg BW is recommended once a week for 8 weeks. It is contraindicated in severe conditions. PQ is difficult to give since the dose is according to age in years which might result in under dosing for same age but larger-sized patients.

Uncomplicated falciparum malaria in pregnant women is treated with oral Quinine only. Oral Quinine and Clindamycin are second-line drugs for treatment failure in pregnant women. Parenteral quinine and Clindamycin is given for severe falciparum malaria. Chloroquine is given for vivax malaria, and also for prevention and treatment of relapses. For mixed infections (falciparum and
vivax), Artemether+Lumefantrine is given for falciparum malaria and Primaquine is withheld until delivery. Relapses are treated with Chloroquine.

AL is the first-line drug of choice for severe malaria. If AL is not available or there is impaired consciousness or treatment failure, Quinine plus (Tetracycline/Doxycycline/Clindamycin) is given. Rectal Artesunate is indicated when there is impaired consciousness or if the health facility does not have resources for parenteral or administration via a naso-gastric tube (NGT). However, this drug is not yet registered in the national drug formulary. The treatment guidelines for falciparum malaria have changed through the years and shifted to AL in 2009 following the results of the TES.

TES for first-line antimalarial drugs has been conducted in Palawan since 2009 for Chloroquine against \( P_v \), and since 2005 for AL against \( P_f \). A new province (Tawi-tawi) will be included in TES studies from August 2014. PQ efficacy was tested in Palawan from 2009 to 2012. All studies follow the WHO protocol and are conducted by the Research Institute for Tropical Medicine (RITM) and local health offices. Funding comes from the Department of Health (DOH), Global Fund and WHO.

\( P_f \) treated with AL showed 98.8% ACPR among those that completed the 28-day follow-up. PCR correction is ongoing. Drug resistance markers being tested are Pfert, Pfδhps, Pfδhps. For CQ against \( P_v \), 166/166 who completed 28 days showed ACPR. PCR correction is also ongoing and the drug resistance marker being tested is PvmDr. For PQ, 95 out of 119 enrolled completed the 28-day follow-up. Molecular work is ongoing; 17 had recurrence of parasitemia over a 6-month period follow-up.

Bottlenecks include difficulty in getting enough samples and the lack of dedicated field-based staff. The financial allocation from the DOH since 2013 has improved. Remaining challenges include limited laboratory equipment and infrastructure of the RITM parasitology department and the limited capacity of the two provinces to carry out TES activities.

The Philippines expects the Pacific Network to be a venue for discussion, data sharing and collaborative work with other countries in the Region. Establishment of surveillance of circulating genotypes and drug-resistant markers is one suggestion for improving TES in the Philippines.

Other operational research includes malaria diagnostic tests – fluorescent in-situ hybridization (FISH) in Palawan, other antimalarials – Phase III clinical trial of Tafenoquine to start third quarter 2014, and G6PD enzyme deficiency prevalence and screening tests performance. The final technical report submitted to the Asia Pacific Malaria Elimination Network and the manuscript are being prepared.

Discussion clarified that the Philippines does not have the capacity to do in vitro so this is not done for parasite failure after 28 days on CQ. It was suggested that recruitment for \( P_f \) be done alongside the conduct of the TES for \( P_v \) in Palawan and that longer follow-up for \( P_v \) be done. Patient recruitment and follow-up is done through community health volunteers (using their mobile phones). They also give incentives to patients so they can go back for follow-up.

2.5.2 Malaysia

Dr Mohd Hafizi Bin Abdul Hamid presented on behalf of his country programme. Malaria has been declining from 12,780 cases in 2001 to 3,850 cases in 2013, with a slight peak in 2008 and decline since then. The number of deaths is also on a downward trend over the same period, from 46 in 2011 to 14 in 2013 (Figure 4). Dr Hafizi reported that cases of \( Plasmodium knowlesi \) is increasing with seven of 14 deaths in 2013 due to \( P_k \).
Malaysia has all five species – *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium knowlesi*, *Plasmodium malariae* and *Plasmodium ovale*, with currently *Pk* having the most number of cases. Of the 3850 cases in 2013, 28% are indigenous cases (human malaria), 23% are imported and 49% are zoonotic. The states of Sabah (0.468) and Sarawak (0.390) have the highest API relative to the national API of 0.130.

A 1996 unpublished report showed 29.4% treatment failure of SP, and 100% sensitivity to Mefloquine and Quinine. There has been increasing failure of CQ-SP over the past decade and by 2013, they started the national drug resistance surveillance of AL and Artesunate-Mefloquine – a hospital-based surveillance.

The national guidelines on treatment for malaria were developed in 1994 and revised in 2000. The national antibiotic guideline was developed in 2008 and the management guidelines of malaria in Malaysia in 2013. Uncomplicated *Plasmodium falciparum* infection is managed with Artemether +Lumefantrine. For pregnant patients, oral Quinine with oral Doxycycline is given for 7 days. Primaquine 0.75mg/kg (max 45 mg) is given on Day 1 of treatment in addition to artemisinin regime and quinine, except for pregnant women and infant under 1 year.

Non-complicated *Plasmodium vivax/ovale* infection is treated with oral Chloroquine and Primaquine. With treatment failure or suspected Chloroquine resistance, it is recommended to repeat the course of AL for 3 days and Primaquine 30 mg OD for 14 days or ACT (artesunate + mefloquine) for 3 days or oral Quinine for 7 days and Primaquine for 14 days.

Recommended drug for non-complicated *Plasmodium malariae/knowlesi* infection is 20 mg artemether/120 mg lumefantrine following a 3-day treatment schedule with 6 doses is recommended, or Artesunate /Mefloquine following 3-day treatment schedule, once daily regime. An alternative is oral Chloroquine.

Ongoing TES studies are testing Artemether Lumefantrine against *P falciparum*, *P knowlesi* and *P malariae*, and are all hospital-based. They started in August 2013 and are expected to be completed by July 2014. The Ministry of Health is the implementing institution and funding source. These studies do not follow the WHO standard protocol for TES. PCR laboratories are the IMR and National Public Health Laboratory.

Problems include the lack of coordination between hospital and district health office, the limited number of cases and data quality (completeness of data).
Programme improvements include SOPs in the new treatment guidelines and training on these guidelines conducted at the national and state level. After consultation with WHO Regional Office for the Western Pacific, TES was suggested to start in specific sentinel sites following WHO protocol. A National Technical Meeting (NMESP) will be held on 15–17 July 2014 to develop the technical plan for this.

Discussion clarified that Malaysia has a hospital-based surveillance system with a cutoff of 100,000 parasitemia as inclusion criteria. The patient stays in the hospital for the entire duration of treatment (up to Day 7) and is monitored by a health inspector. Follow-up is done until Day 56. Slides are also collected during follow up. Hospital-based surveillance is a different way of monitoring therapeutic efficacy. With this method, the patient's place of residence is unknown, resulting in a blank estimate of results for the country and there could be many losses to follow-up as patients go back to the jungle upon discharge from the hospital. Malaysia will use volunteers to help with follow-up. For *Pk*, microscopy is used for diagnosis. Patients with microscopy diagnosis of *Pk* or *Pm* have their blood films confirmed by PCR. There are five PCR laboratories in Malaysia.

### 2.5.3 Indonesia

Dr. Marti Kusumaningsih presented the update. API has been decreasing from 4.68 in 1990 to 1.37 in 2013. Among the provinces, Papua (38.44), NTT, and Kalimantan have the highest incidence (higher than the national API of 1.37). Over the past four years, the proportion of districts/municipalities that have API less than 1 has been increasing.

The national drug policy had artesunate-amodiaquine as the first line ACT for *P. falciparum* malaria in 2004. This was later expanded in 2006 to also cover *P. vivax* malaria. In 2008, the use of DHP was initiated in Papua.

The current drug policy has the following treatment options for uncomplicated *Pf*:
1) dihydroartemisinin (DHA) and piperaquine (PPQ) plus PQ,
2) artesunate (ATS) plus amodiaquine (AQ) plus PQ,
3) Quinine (QN) plus doxycycline (DX)/Clindamycin plus PQ, and
4) AL plus PQ. Complicated and severe malaria is treated with parenteral artesunate DHA and PPQ plus PQ, or intramuscular artemether or quinine (parenteral or oral) plus doxycycline or clindamycin and PQ. Drug of choice for vivax malaria is DHA and PPQ plus PQ, or ATS and AQ plus PQ, or QN and DX/Clindamycin plus PQ.

Clinical trial of oral ACT is being conducted in 9 sites. Among the artemisinin drug combination studied for *Pf*, artesunate-amodiaquine showed 84-93.8% ACPR (with PCR correction). AL and artesunate piperaquine showed 99 and 96.5% ACPR (with PCR correction), respectively (Table 1). Among the ACTs for *Pv* studies, AL fared the worst (43% ACPR) and artemisinin naftoquinone the best at 98.7%.

<table>
<thead>
<tr>
<th>ACT</th>
<th>FCT (hours)</th>
<th>PCT (hours)</th>
<th>ACPR non PCR (%)</th>
<th>ACPR with PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS3+SP1*</td>
<td>32</td>
<td>32</td>
<td>93.3</td>
<td>95.6</td>
</tr>
<tr>
<td>ATS3+AQ3</td>
<td>26.4</td>
<td>28.8</td>
<td>78.0-95.0</td>
<td>84-93.8</td>
</tr>
<tr>
<td>(ART+PPQ)2*</td>
<td>24</td>
<td>33.6</td>
<td>100</td>
<td>96.5</td>
</tr>
<tr>
<td>(ATM+LMF)3</td>
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<td>24</td>
<td>96.1-97.2</td>
<td>99.2</td>
</tr>
<tr>
<td>(DHA+PPQ)3</td>
<td>11.3</td>
<td>25.5</td>
<td>96.8</td>
<td>95.2-97.0</td>
</tr>
<tr>
<td>(ATS+PD)3</td>
<td>15.9</td>
<td>23.9</td>
<td>98.9</td>
<td>99.5</td>
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<td>(ART+NTQ)1</td>
<td>8</td>
<td>24</td>
<td>98.7</td>
<td>98.7</td>
</tr>
</tbody>
</table>

Table 1. Therapeutic efficacy study results for ACT against *P. falciparum* in Indonesia, 2009.

Other research currently include falciparum phenotyping from West Suma during 42 day follow-up which showed 88.2% ACPR (N=110). The TES proposal for the year is under ethical review.
Other issues include: local capacity-building at regional level to conduct the study, antimalaria drug surveillance as a part of MCP, and needs for sustained budget from Government, mechanisms for sustained drug quality monitoring and pharmacovigillance and strengthening networks among research institutions and national programmes.

Discussion included that the DHAP product that the country programme is using is not pre-qualified. The WHO-approved formulation is Sigmatar. Concern was raised about the less than optimal ACPR of artesunate-amodiaquine. Artesunate-amodiaquine is better in Sumatra than in Papua; DHP may have a similar profile. AL for \( P_v \) has 43% ACPR. This shows that the current system is not appropriate for \( P_v \) as it cannot differentiate relapse from recrudescence. A better system of way of presenting the information needs to be developed using the ACPR classification.

### 2.5.4 Solomon Islands

Dr Lyndes Wini presented the update. The malaria burden is centrally located within the groups of islands. From 2000 to 2012, there has been a more than 70% reduction in API and more than 90% reduction in reported malaria mortality. By 2013, the API has been reported to be 1.43 per 1000 with 18 deaths.

The treatment for uncomplicated malaria is AL for \( P_f \) and AL plus PQ at 0.25 mg/kg BW for \( P_v \). Severe malaria is treated with artesunate injectable with quinine as the second line. Malaria in pregnancy is managed with quinine for 7 days for the first trimester and AL for the second and third trimester. CQ is recommended for chemoprophylaxis in pregnancy.

The efficacy of chloroquine has been on a decline since 1984, and even with the CQ+SP combination, there was 88% ACPR seen in 2005. This prompted the shift to AL in 2009.

They have rotating TES sentinel sites which are located in Auki, Malaita Province and Tetere, Guadalcanal Province. Selection of these sites was based on disease burden. All have completed field samples but there are still no proposed sites for 2014.

TES results obtained from 2008 to 2013 show that AL efficacy against \( P_f \) is good in both Auki and Tetere sites. For \( P_v \), AL efficacy in Tetere is better than in Auki (94% vs 74%) (Table 2), although the number of patients completing the trials were relatively small in Auki. PCR positivity for \( P_v \) from day 14 to 28 showed 9.2% on day 14, and 45.3% on Day 28. The results have not been published to date.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasite species</td>
<td>( P_f )</td>
<td>( P_v )</td>
<td>( P_f )</td>
<td>( P_v )</td>
</tr>
<tr>
<td>Name of sentinel site</td>
<td>Auki</td>
<td>Auki</td>
<td>Tetere</td>
<td>Tetere</td>
</tr>
<tr>
<td>No. of patients enrolled</td>
<td>19</td>
<td>23</td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td>No. of patients completing</td>
<td>18</td>
<td>23</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>28 days of follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with ETF</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. of patients with LTF</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No. of patients with LCF</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No. of patients with ACPR</td>
<td>17 (0.944)</td>
<td>17 (0.739)</td>
<td>24 (1)</td>
<td>56 (0.949)</td>
</tr>
</tbody>
</table>

Table 2. Therapeutic efficacy study results in Solomon Islands, 2011 to 2013
There is now better coordination in doing the TES, however the changing malaria epidemiology has affected recruitment rates at sentinel sites, particularly for the *Pf* arm. Human resources remain an issue in the face of competing activities. Solomon Islands expects the network to facilitate improved collaboration among partner countries and with partner institutions.

For other studies, Solomon Islands plans to start the Primaquine Safety and Efficacy Study in 2014 and the G6PD deficiency prevalence study which might be nested into the PQ Study.

Discussion included that the accuracy and reliability of data has improved compared to previous years. Detection of cases should be by microscopy. There was a substantial difference between positivity of *Pv* by microscopy and by PCR. Sub-microscopic infections could show up later and raised the possibility of these patients carrying heavily selected (or resistant) parasites. It could be recrudescence but with lower parasitemia. For TES, PCR correction is not intended to correct for the microscopy results but to correct for relapse and reinfection. On the distribution of G6PD deficiency, Isabel has 15% in some studies. They still recommend PQ and ask the patients to monitor their urine. Physicians are still reluctant to prescribe this even at a low dose.

### 2.5.5 Vanuatu

The update was presented by Mr Esau Naket. Malaria cases followed an upward trend from 2000 to 2003, after which there was a steep decline, followed by an increase from 2008 to 2010 (possibly related to a roll out of RDTs for diagnosis), then decreased thereafter until 2013 (Figure 5).

Uncomplicated malaria is treated with AL for *P. falciparum* and *P. vivax* plus PQ for *P. vivax*. Parenteral artesunate is the drug of choice for severe malaria. For malaria in pregnancy, QN oral or as an intravascular infusion is given for the first trimester, AL for the second and third trimester. Weekly chloroquine is recommended for chemoprophylaxis in pregnancy.

Mr Naket recounted how CQ resistance was documented early in the 1980s. CQ+SP was adopted for *P. falciparum* in 1991. TES done in 2005 over 28 days (Kinzer et al., 2010) still showed 100% efficacy of CQ against *Pv* and 97% for CQ+SP against *Pf*.

TES was done from 2011 to 2012 in one sentinel site – Vaemali Health Centre on Epi Island, Shefa province. Following the WHO protocol, the study was implemented by the MOH and WHO and funded by GF, with PCR genotyping done by AMI. TES results showed 98.8% of patients who
completed the 28-day follow-up had ACPR for the $Pv$ arm of the AL study. No $Pf$ patients were detected in one year.

TES was attempted in 2013 in a sentinel site on Santo Island, Sanma Province, as part of a trial of primaquine against relapsing vivax-malaria. The study was implemented by MOH, WHO and colleagues form the Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne, with funding from Global Fund and AusAID. Results for the $Pv$ arm are still not available pending the genotype PCR results. Again, like in the TES conducted on Epi Island in 2011-2012, no single patients were enrolled for the $Pf$ arm, pointing to a very low level of Pf malaria in Vanuatu.

In 2014, a health facility survey is being conducted in 40 health centres and hospitals in Vanuatu on the readiness and observed management of fever.

Bottlenecks to TES implementation include the absence of a local research institution and the dramatically decreasing number of malaria cases, in particular Pf, which makes TES almost impossible to implement nowadays.

Discussion on progress, bottlenecks and way forward

Malaria incidence and deaths in the five countries are all on a downward trend. For treatment policy, all are using ACTs for $Pf$. Only Malaysia and the Philippines are using CQ for $Pv$. Malaysia has also included ACT for $Pk$ and $Pm$.

Most of the countries have conducted TES for $Pf$ and $Pv$. Common bottlenecks include difficulty in getting samples because of the low number of cases, site selection, human resource constraints and the issue of primaquine use and G6PD deficiency.

A recommendation was made to highlight in future the proportion of cases that have a delay in Day 3 clearance, as this is an early indicator of treatment failure. There is growing commitment and support from partners and donors—financial, programmatic as well as technical.

Dr Vestergaard gave an update on Papua New Guinea. TES was done by the PNG Institute for Medical Research (IMR), with funding from the Global Fund in support of monitoring and evaluation activities of the national malaria control programme. But as TES is often implemented within other clinical trials done by IMR, the national program has faced problems in obtaining timely access to the TES data. Currently, there is still no clear decision on who should do TES. The bottleneck is the absence of definite key people to do the TES. Dr Qin of the Australian Army Malaria Institute (AAMI) in Brisbane offered help to support TES with parasite genotyping, i.e. similar to what has been done by AAM for the national malaria programmes in the Solomon Islands and Vanuatu.

Common issues across Network countries include identifying an institution to carry out the TES and ensuring adequate institutional capacity. The Indonesian national program intends to assign Regional Center for Technical and Environmental Health (BBTKL) to conduct the TES but they are still not ready to do so. In the Philippines, RITM is responsible for research and TES in particular, but human resource remains a constraint for them also. Their strategy is to focus on training of local health staff. In Malaysia, ownership has been under IMR since 2003 but implementation is being done by MoH staff. But with internal problems since 2007, TES was temporarily shelved. Starting 2013, MOH had initiated the resumption of TES, in coordination with IMR but the focal entity is the MOH.

For Solomon Islands, the programme has been collaborating on TES with AAMI, but is now working with WEHI. Initial capacity building in the country focused on strengthening microscopy and
following the protocol. With the possibility of termination of GF funding soon, they already have trained people in sentinel sites, but there has to be regular monitoring. The external competency assessment (ECA) programme of WHO has helped them develop and maintain a pool of trained and certified microscopists.

Assistance to countries should be harmonized to meet their needs, particularly in the context of other initiatives and networks. The WHO ERAR programme can provide support such as training to countries and to increase surveillance outside the Greater Mekong Subregion. For countries with Global Fund support, technical assistance support can be complemented by ERAR.

Initiatives or measures to monitor risk or enabling factors such as endorsement of monotherapy ban and its actual implementation are also important. This is part of the response in the Greater Mekong Subregion with surveys largely conducted by PSI.

2.6 Technical session 6: update on the K13 marker and working definition of artemisinin resistance

Dr Vestergaard defined antimalarial drug resistance as the “ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject” (WHO, 1973).

Therapeutic efficacy is used as an "alert" to drug resistance but not all treatment failures are due to resistance. Treatment failure can be due to pharmacokinetics (low absorption, increased metabolism, etc.), immunity (HIV, pregnancy, etc.) and confirmed resistance. This is why other tools are needed to confirm resistance such as pharmacokinetic studies, in vitro parasite studies and molecular markers.

The parasite clearance estimator (Figure 6) measures how quickly parasites disappear after treatment, which is correlated with the results of clinical monitoring. The main effect of artemisinin resistance is on the slope of the log-linear decline and for this reason this tool has focused on this variable. Results for a study are expressed in median slope half-life. The slope is not influenced by initial parasitaemia. It does take into consideration the lag and tail phases but complicates the clearance estimation.

![Figure 6. Parasite clearance estimator](image-url)
A molecular marker of artemisinin-resistant \( Pf \) malaria has been found through laboratory induced resistance—the Kelch 13 mutation. Most Kelch 13 mutations (SNPs) reside in the "propeller" domains. Graphs indicating frequency of K13-propeller SNPs in 886 parasite isolates in six Cambodian provinces from 2001 to 2012 showed them to be prominent in the provinces of Paillin, Battambang, Pursat (Western Cambodia) and Kratie.

The proposed new definition of artemisinin resistance is; for suspected resistance, it is either 5% K13 domain mutants or 10% day 3/slope > 5 (ACT or AS monotherapy). For confirmed resistance, it is 5% infections with both Kelch domain mutation (which were confirmed to be related to either delayed clinical clearance or delayed RSA) and 10% day 3/slope > 5 (ACT or AS monotherapy)

Several confounding factors include slow clearance, absence of the mutant gene, low immunity, splenectomy or insufficient blood levels of antimalarial drugs. Normal clearance and presence of mutation, on the other hand, may actually be found in a state of high immunity (as seen in Africa). Definitions of artemisinin resistance could still change over time with new information on K13 mutations becoming available. A revised new definition of ACT resistance is the presence of artemisinin resistance as defined previously; and presence of partner drug resistance = treatment failure + adequate blood level (if known) and/or presence validated molecular marker of resistance (if known). Treatment failures with or without day 3 will NOT systematically be defined as ACT resistance as many factors can affect the efficacy of the partner drug such as drug absorption and metabolism.

In summary, K13 mutations provide a potentially powerful new molecular marker of artemisinin resistance which has been found to be associated with delayed parasite clearance in Cambodia, Viet Nam and Myanmar. Many K13 mutations exist which are very strongly - but not always - related to slow parasite clearance after artesunate treatment. Artemisinin resistance appears to be both spreading and emerging independently. More work is needed to understand and clarify the use of the new K13 marker to monitor artemisinin resistance.

2.7 Technical session 7: presentation of group work: country malaria drug resistance monitoring plans 2014–2015

Dr Vestergaard introduced the group work of developing plans for 2014–2015. Countries were requested to use a planning template and look at the previous year's plans to check what was achieved, identify gaps, needs and proposed budget for each of the sites. A new column was added to include information on microscopy and validation status in the country. He said that funding is available from ERAR to support TES activities.

2.7.1 Philippines

A \( Pf \) and \( Pv \) TES study has been ongoing since July 2013 in south Palawan. While the \( Pf \) arm has achieved the target sample size, the \( Pv \) arm needs 10 more patients. A new site (in Tawi-tawi) will be added this year to test AL for \( Pf \) and CQ for \( Pv \). Funding for TES comes mostly from the national programme budget, with Global Fund finances covering part of budget for the \( Pv \) arm of the Palawan study. The implementers are the local health units of the study site municipalities, the RITM and the DOH. The first and second slide readers will be the RHU medical technologists and the validators (cross-checkers). The TES monitoring is done by RITM. The Philippines has 19 level 1 microscopists and three level 2 microscopists. RITM will provide the laboratory support.

TES support needs identified include: 1) APMEN funding for some specific parasite genotyping work (parasite bioinformatics project), 2) AAMI for technical advice and support of molecular work, 3) Human resources for data management, 4) Development of report template, and 5) Development of SOPs and report forms for monitoring.
For 2015, the plan is to establish collaborating centres – which are actually regional health offices of the DOH – to function as lead for TES implementation. The Pf and Pv studies in Tawi-tawi will be continued. DOH/RITM will also explore trying to set up with a private health facility (Rio Tuba Nickel Foundation Inc. Hospital) to facilitate Pv studies in the southern municipality of Palawan. Funding for the above studies will come from the DOH except for the proposed collaboration with the private hospital which will be funded by the Foundation. Implementers are the same as those in 2014. They plan to form a pool of TES monitors composed of staff with formal medical and paramedical training. The need for refresher microscopy training is assessed every three years and will be addressed as necessary. The last refresher training for the medical technologists involved was in 2012.

For their plan to tie up TES to the establishment/strengthening of collaborating centers which will eventually be responsible for conducting the TES, they would need technical input on how to set this up and maintain operations. They also expressed the need for technical assistance on data analysis and reporting.

**2.7.2 Solomon Islands**

For 2014, Solomon Islands will conduct TES in one site (Tetere) and will test for drugs for Pf and Pv; The estimated cost is US$ 12,500 and will come from WHO. The implementer is MHMS, with the VBDME microscopists as the first and second slide readers. The Pacific Network will provide the TES monitoring. Their microscopists need refresher training. Solomon Islands currently have two level 1, and seven level 2 microscopists. Laboratory support will be provided by AAMI (for microscopy) and WEHI (for PCR). They need help with technical report writing. Their plans for 2015 are the same as those for 2014, except that the TES site will likely be in Kira Kira.

During the discussion that followed, Dr Christophel emphasized that issues of Pv treatment needs to be a priority, given the high frequency of relapsing strains of Pv in the country.

**2.7.3 Vanuatu**

Vanuatu has no definite plans for TES in 2014-2015. The current very low level of malaria transmission in the country, thanks to intensive malaria control efforts over the past five years, makes TES implementation very difficult, in particular with respect to falciparum-malaria. There are simply very few cases to enroll in TES. Another challenge is the lack of adequately trained health personnel in the country. A key priority would be to build up the capacity of the existing human resource. One major challenge is the absence of a local institution to do the TES. Another round of microscopy ECA was just done this year. They have one level 1 microscopist and three level 2 microscopists.

Dr Vestergaard affirmed support from the network for the identified needs. National malaria programmes may provide their schedule of trainings within their respective countries so that participants from neighboring countries can also participate, thus allowing inter-country collaborations and exchanges, e.g. between Vanuatu, Solomon Islands and Papua New Guinea, sharing similar challenges.

**2.7.4 Malaysia**

TES in 2014 will have two sites, Sabah and Sarawak, and will test AL for Pf and forPk, respectively. Funding will come from the MOH operations budget and they will inform the Pacific Network if additional support is needed. The implementers are MOH and National Public Health Laboratory (NPHL) with the first slide reader from the state laboratory, and the second slide reader from NPHL (Sabah). The Western Pacific Region Drug Resistance Coordinator will act as external monitor and
the MOH/NPHL as the internal TES monitor. Refresher microscopy training is done three times a year by the NPHL.

Malaysia currently has three level 1 microscopists and seven level 2 microscopists. Laboratory support will be provided by IMR and NPHL. They will be coordinating with Sabah and Sarawak State Vector Offices and sentinel hospitals.

For 2015, they will retain the two sites but they will test artemunate-mefloquine for \textit{Pf} and \textit{Pk}. Arrangements and other implementation details will be the same as in 2014. They expressed their need for technical support in setting up (using WHO protocol), and also with reporting.

2.7.5 Indonesia

For 2014 to 2015, Indonesia will have six sites and test for DP for \textit{Pf} and \textit{PV}. They estimate a funding requirement of US$ 240 000, which will come from WHO. The MOH and Eijkman Institute are the implementing agencies, with the first and second slide readers coming from the PHC and Eijkman. Support for refresher microscopy training, ECA and external monitoring were requested from WHO.

For 2015–2016, they plan to conduct TES in six new provinces. They estimate the same budgetary requirements and propose to get this from the MoH, WHO and Global Fund. They will have the same arrangements for implementers, slider readers and TES monitor and will continue to require refresher training for their microscopists. By 2016, they project that all would be post-ECA certified microscopists.

In the discussion that followed, Dr Guintran pointed out that every country should be clear regarding the process for certification, and encouraged countries to put in a place a routine QAS run by a national reference laboratory.

3. CONCLUSION AND RECOMMENDATIONS

Dr Christophel presented the draft conclusions and recommendations.

3.1 Conclusions

Since the last Pacific Network meeting in May 2013, not all seven countries in the network could carry out TES according to the WHO protocol. The network should play a strong role in: capacity-building, supporting implementation, quality control, coordination, information sharing/dissemination and intercountry exchange. A candidate molecular marker for artemisinin resistance is now available, which could be included in the TES. The network could help coordinate and validate this marker in the Pacific. TES results for \textit{P. vivax} were not conclusive for some countries due to high frequency of relapsing \textit{Pv} strains.

3.2 Recommendations

1) Of high priority for all seven countries of the network is to carry out high-quality TES of their national first-line malaria treatment regimens for \textit{Pf}, \textit{PV} (and \textit{Pk} in Malaysia) in the next year, following WHO standard protocol including analysis of day 3 positivity data (indicator for artemisinin resistance) as part of the TES, based on the updated and agreed plans for 2014–2015.
2) The network should support countries in TES planning and implementation, particularly in:
   a. Building capacity, including through intercountry exchanges:
      i. regional PI training [TES preparation and implementation training for TES teams and
         microscopists will take place at national level, to be included in the TES protocol
         budget], within the next three months; and
      ii. regional writeshop for TES reports and/or manuscripts.
   b. Provide TES implementation support, including:
      i. provision of quality controlled study drugs;
      ii. topping up country operational budgets if needed;
      iii. sharing SOPs (e.g. for the filter paper collection for genotyping and K13 testing, data
           entry/management), report forms and checklists;
      iv. supporting analysis and reporting (including providing a reporting template);
      v. laboratory support: molecular work: AMI (the Philippines, Solomon Islands, Vanuatu,
         Timor Leste), RITM, Malaysia NPHL and IMR, Eijkman Institute, WEHI.
   c. Quality assurance of TES, including:
      i. clinical monitoring of TES (including establishing a roster of monitors);
      ii. organize regional ECA (including microscopists from research institutions involved
          in TES and clinical trials) for a pool of possible TES microscopists;
      iii. sharing of microscopy expertise among countries, e.g. for validation of TES slides;
      iv. facilitate establishing a EQA system for genotyping (AMI at least 1 round).
   d. Coordination, information sharing and support for publications (e.g. technical review, fees).
   e. Engage partners where it benefits the network (e.g. Mekong network) and mobilize resources.

3) Countries should ensure high quality microscopy results through involving their level 1
   microscopists (based on external competency assessment) as part of the TES team, and strengthen
   their national malaria microscopy QA systems where needed.

4) Encourage implementation research that contributes to:
   a. improved TES (e.g. for selection of sentinel sites, private facility inclusions);
   b. treatment guideline implementation (e.g. monitoring of the safety of primaquine for \( P_\text{v} \) in
      Solomon Islands and Papua New Guinea, with high frequency relapsing \( P_\text{v} \) strains);
   c. detection/prevention of artemisinin resistance (e.g. antimalarial drug quality/availability
      surveys).
3rd PACIFIC MALARIA DRUG RESISTANCE MONITORING NETWORK MEETING
16-17 June 2014 – Manila, Philippines

TIMETABLE

DAY 1 (Monday 16 June 2014)

08:00 – 08:30  Registration
08:30 – 08:50  Opening session  Dr Mark Jacobs Director
                Combating Communicable Diseases, WPRO
08:50 – 09:00  Objectives of the meeting  Dr Eva Christophel, WHO/WPRO
09:00 – 09:20  Update on tracking and mapping of antimalarial drug efficacy and drug resistance globally and in the Western Pacific Region  Dr Lasse Vestergaard, WHO/WPRO
09:20 – 09:40  Update on antimalarial drug resistance in the South East Asian Region  Dr Maria Dorina Bustos, WHO Thailand
09:40 – 10:00  The Emergency Response to Artemisinin Resistance (ERAR)  Dr Eva Christophel, WHO/WPRO
10:00 – 10:30  Group photo and coffee/tea break
10:30 – 11:30  Update on the new 2014 WHO TES template and use of the new excel data entry tool  Dr Maria Dorina Bustos, WHO/SEARO
11:30 – 12:00  Plenary discussion: country inputs to above updates  Facilitator: Dr Qin Cheng, AAMI, Australia
12:00 – 13:00  Lunch
13:00 – 14:30  Country updates: Current treatment policy, latest drug efficacy results for P falciparum and P vivax, technical issues and challenges, updates on operational research and other initiatives, survey data on malaria case management (20 minutes/country)  Chairperson, country representatives
14:30 – 15:00  Coffee/tea break
15:00 – 16:00  Resume country updates  Chairperson, country representatives
                Papua New Guinea
                Solomon Islands
                Vanuatu
16:00 – 17:00  General discussion on progress, bottlenecks and way forward  Facilitator: Dr Emiliana Tjitra, NIHRD, Indonesia
17:00  Closure of day 1
**DAY 2 (Tuesday 17 June 2014)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Facilitator/Remarks</th>
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<tbody>
<tr>
<td>08:30 – 09:00</td>
<td>Updates on the Kelch-13 molecular marker of artemisinin resistance</td>
<td>Dr Lasse Vestergaard, WHO/WPRO</td>
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<td>09:00 – 09:15</td>
<td>Introduction to group work on 2014-15 country TES plans</td>
<td>Dr Lasse Vestergaard, WHO/WPRO</td>
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<td>09:15 – 10:00</td>
<td>Group work, by country, on 2014-2015 TES plans</td>
<td>Facilitators: WHO country focal points</td>
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<td>10:00 – 10:30</td>
<td><em>Coffee/tea break</em></td>
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<tr>
<td>10:30 – 12:00</td>
<td>Continued Group Work on 2014-2015 TES plans + prepare country presentations</td>
<td>Facilitators: WHO country focal points</td>
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<tr>
<td>12:00 – 13:00</td>
<td><em>Lunch</em></td>
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<tr>
<td>13:00 – 14:20</td>
<td>Plenary: Presentation and discussion of country plans (20mins/country)</td>
<td>Chairperson, country representatives</td>
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<td>Philippines</td>
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<td>14:20 – 14:50</td>
<td><em>Coffee/tea break</em></td>
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<td>14:50 – 15:50</td>
<td>Malaysia, Indonesia, East Timor</td>
<td>Chairperson, country representatives</td>
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<tr>
<td>15:50 – 16:50</td>
<td>Recommendations on the way forward, discussion on the role of the Pacific Network, coordination with partners etc.</td>
<td>Dr Lasse Vestergaard, WHO/WPRO</td>
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<tr>
<td>16:50 – 17:00</td>
<td>Closing session</td>
<td>Chairperson, WHO WPR and SEAR Representatives</td>
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</table>
ANNEX 2

LIST OF PARTICIPANTS,
TEMPORARY ADVISERS, REPRESENTATIVES/OBSERVERS
AND SECRETARIAT

Dr Marti Kusumaningsih, Directorate General of Disease Control and Environmental Health,
Sub-directorate of Malaria, Jl Percetakan negara 29, Jakarta, Indonesia. Tel. No: +62 21 7323850,
Email: kus_sumarsono@yahoo.com

Dr Din Syafruddin, Senior Research Fellow and Head of Malaria and Pathogen Resistance Labatory
Eijkman Institute for Molecular Biology, Jl. Diponegoro 69, Jakarta, Indonesia.
Tel. No: +603-8883 4268, Email: din@eijkman.go.id

Dr Mohd Hafizi Abdul bin Hamid, Principal Assistant Director, Disease Control Division,
Ministry of Health Malaysia, Level 4, Block E10, Parcel E, Federal Government Administrative
Complex, Putrajaya, Malaysia. Tel. No: +603 8883 4268 / +6012 359 0017

Dr Mario Baquiloc, Medical Officer V/In Charge of Infectious Diseases Office,
National Center for Disease Prevention & Control, Department of Health, San Lazaro Compound,
Manila, Philippines. Tel. No: +632 997 3399, Email: marbaquiloc@yahoo.com

Dr Fe Esperanza Caridad Espino, Medical Specialist III, Head, Department of Parasitology and
National, Reference Laboratory for Malaria and other Parasites, Research Institute for Tropical
Medicine, Filinvest Corporation, Alabang, Muntinlupa City, Philippines.
Tel. No: +632 807 2628 to 32, loc 227/804, Email: fe.espin02012@gmail.com

Dr Albino Bobogare, Director, National Vector Borne Disease Control Programme,
Ministry of Health and Medical Services, P.O. Box 349, Honiara, Solomon Islands.
Tel. No: +677 39748/30655, Email: A47bobogare@gmail.com

Dr Lyndes Wini, Medical Officer, Vector Borne Disease Control Programme,
Ministry of Health, P.O. Box 349, Honiara, Solomon Islands. Tel. No: +677 30410
Email: lyndes.wini@gmail.com

Mr George Taleo, Malaria Programme Manager, Ministry of Health, PMB 909
Port Vila, Vanuatu. Tel. No: +678 22512, Email: gtaleo@vanuatu.gov.vu

Mr Esau Naket, Malaria Nurse Practitioner, National Malaria Control Programme,
Ministry of Health, PMB 9009, Port Vila, Vanuatu. Tel. No: +678 7752427,
Email: enaket@vanuatu.gov.vu

Dr Qin Cheng, Head, Drug Resistance and Diagnostics, Army Malaria Institute,
Gallipoli Barracks, Enoggera, Brisbane, Australia. Tel. No: +617 3332 4834
Email: qincheng@defence.gov.au

Dr Emiliana Tjitra, Senior Researcher, Center for Applied Technology of Health and
Clinical Epidemiology, National Institute of Health Research & Development,
Ministry of Health, Jl. Percetakan Negara No. 29, Jakarta 10560, Indonesia.
Tel. No: +62 21 3102849, Email: emilt@litbang.depkes.go.id / etjitra@yahoo.com
## COUNTRY TES PLANS

### Philippines, 2014

<table>
<thead>
<tr>
<th>Name of TES site</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
<th>Funding source</th>
<th>Implementer(s)</th>
<th>1st and 2nd slide reader</th>
<th>TES Monitor</th>
<th>Refresher microscopy training needs (&gt;20% discordance in results by col F)</th>
<th>Number of Level 1 and Level 2 Microscopist in country</th>
<th>Laboratory support</th>
<th>Other needs/gaps</th>
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</thead>
<tbody>
<tr>
<td>Palawan (March-December 2013; ongoing lab work)</td>
<td>(Pf - AL)</td>
<td>GoP</td>
<td>Bataraza RHU, Brooke's Point RHU, RITM, Malaria Program</td>
<td>RHU medical technologists and validators (cross-checkers)</td>
<td>Dr. Lasse Vestergaard and Ms. Arlene Leah Santiago</td>
<td>Assessed every three years; addressed when necessary; last for MTs was 2012</td>
<td>Level 1 = 19 Level 2 = 3</td>
<td>RITM</td>
<td>1. APMEN for data analysis (parasite bioinformatics); report</td>
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<td>Palawan (March 2013 - December 2014)</td>
<td>(Pv - Cq)</td>
<td>GoP/ GF</td>
<td>Bataraza RHU, Brooke's Point RHU, Rizal RHU, RITM, Malaria Program</td>
<td>RHU medical technologists and validators (cross-checkers)</td>
<td>Dr. Lasse Vestergaard and Ms. Arlene Leah Santiago</td>
<td>Assessed every three years; addressed when necessary; last for MTs was 2012</td>
<td>Level 1 = 19 Level 2 = 3</td>
<td>RITM</td>
<td>2. AAMI for technical advise and support of molecular work</td>
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<tr>
<td>Tawi-Tawi (August - 2015)</td>
<td>(Pf - AL)</td>
<td>GoP</td>
<td>Panglima Sugala RHU, PHO, RITM, Malaria Program</td>
<td>RHU medical technologists and validators (cross-checkers)</td>
<td>Dr. Lasse Vestergaard</td>
<td>Assessed every three years; addressed when necessary; last for MTs was 2012</td>
<td>Level 1 = 19 Level 2 = 3</td>
<td>RITM</td>
<td>3. Human resources (data management)</td>
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<td>(Pv - Cq)</td>
<td>GoP</td>
<td>Panglima Sugala RHU, PHO, RITM, Malaria Program</td>
<td>RHU medical technologists and validators (cross-checkers)</td>
<td>Dr. Lasse Vestergaard</td>
<td>Assessed every three years; addressed when necessary; last for MTs was 2012</td>
<td>Level 1 = 19 Level 2 = 3</td>
<td>RITM</td>
<td>4. Report template</td>
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<td>5. SOPs and report forms for monitoring</td>
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**ANNEX 3**
<table>
<thead>
<tr>
<th>Name of TES site</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
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<th>TES Monitor</th>
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<th>Laboratory support</th>
<th>Other needs/gaps</th>
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<tr>
<td>End-of-year forum to discuss findings and their implications for local stakeholders, program elimination efforts (e.g. program policies) and contribution to regional efforts, etc.</td>
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<td>Tawi-Tawi (continuation)</td>
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<td>Panglima Sugala RHU, PHO, RITM, Malaria Program</td>
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<td>GoP</td>
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<td>RHU medical technologists and validators (cross-checkers)</td>
<td>Monitor pool to be created (formal medical and paramedical training)</td>
<td>Assessed every three years; addressed when necessary</td>
<td>Level 1 = 19 Level 2 = 3 To be updated</td>
<td>Collaborating centers and RITM</td>
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<td>Palawan (updated TES protocol)</td>
<td>Pf - Al</td>
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<td>Bataraza RHU, Brooke's Point RHU, RITM, Malaria Program</td>
<td>RHU medical technologists and validators (cross-checkers)</td>
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<td>Region (CHD) II (Cagayan Valley) as TES coordinating center for Northern Luzon</td>
<td>Pf - AL, Pv - Cq</td>
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<td>Respective RHUs and provincial staff, RITM, Malaria Program</td>
<td>RHU medical technologists and validators (cross-checkers)</td>
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<td>Region (CHD) IVb (Palawan) TES coordinating center</td>
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<td>Explore private health facilities (e.g. Rio Tuba Nickel Foundation, Inc. hospital)</td>
<td>Pf - AL, Pv - Cq</td>
<td></td>
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<td>Health facility staff</td>
<td>Health facility med technologist as reader 1; reader 2 are public sector cross-checkers</td>
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<td>Collaborating centers and RITM</td>
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<td>WEHI (PCR)</td>
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Vanuatu

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Priority.- Capacity building for country team in term (a) coordinator, TES excel, firmilized in Standard SOP & Check List by WHO.
### Malaysia

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<td>MOH operational budget *Additional (WPRO Network)</td>
<td>MOH</td>
<td>MOH/NPHL PI: NPHL officer (Sg Buloh) Co-PI: NVBD officer, IMR officer, Sabah VBD officer</td>
<td>1st : State lab 2nd : NPHL (Sabah) External monitor/WPRO coordinator</td>
<td>MOH/NPHL</td>
<td>3x /year (routine at NPHL)</td>
<td>3 Level 1 7 Level 2</td>
<td>IMR and NPHL</td>
<td>1. Technical Support (Protocol) 2. Coordination with Sabah State Vector Office and sentinel hospital</td>
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* Additional funds from WPRO Network
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