Meeting Report

Second Pacific Malaria Drug Resistance Monitoring Network Meeting

Manila, Philippines
6–7 May 2013

World Health Organization
Western Pacific Region
Participants of the Second Pacific Malaria Drug Resistance Monitoring Network Meeting
Manila, Philippines, 6–7 May 2013
Participants of the Second Pacific Malaria Drug Resistance Monitoring Network Meeting
Manila, Philippines, 6–7 May 2013
REPORT

SECOND PACIFIC MALARIA DRUG RESISTANCE MONITORING NETWORK MEETING

Convened by:
WORLD HEALTH ORGANIZATION
Western Pacific Region

Manila, Philippines
6–7 May 2013
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 Regional Office 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 on 6 and 7 May 2013.
CONTENTS

ACRONYMS AND ABBREVIATIONS

EXECUTIVE SUMMARY

1. INTRODUCTION ....................................................................................................................1
   1.1 Meeting objectives.........................................................................................................1
   1.2 Welcome remarks ..........................................................................................................1
   1.3 Opening remarks ...........................................................................................................1
   1.4 Nomination of Chair, Vice-Chairs and Rapporteur .......................................................2

2. PROCEEDINGS .......................................................................................................................2
   2.1 Technical Session 1: Update on antimalarial drug efficacy monitoring and resistance ................................................................................2
   2.2 Technical Session 2: Country updates on the malaria situation, treatment policy, drug resistance and monitoring, and technical issues .............................................................................6
   2.3 Technical Session 3: Update on technical issues to strengthen drug resistance monitoring .................................................................................................................................11
   2.4 Group Work: Development of Country Malaria Drug Resistance Monitoring Plans .................................................................................................................................13
   2.5 Technical Session 4: Role and modus operandi of the Pacific Malaria Drug Resistance Monitoring Network ........................................................................................................16
   2.6 Technical Session 5: Supportive action .......................................................................18

3. CONCLUSION AND RECOMMENDATIONS ....................................................................20

ANNEXES

Annex 1 - TIMETABLE
Annex 2 - LIST OF PARTICIPANTS, TEMPORARY ADVISERS, REPRESENTATIVES/OBSERVERS AND SECRETARIAT
Annex 3 - COUNTRY TES PLANS
Annex 4 - TES LABORATORY MICROSCOPY WORKSHOP
Annex 5 - FORM FOR SUMMARY OF LABORATORY RESULTS BY PHYSICIAN
Annex 6 - LIST OF DOCUMENTS DISTRIBUTED
Annex 7 - LIST OF DOCUMENTS IN USB
ACRONYMS AND ABBREVIATIONS

ACD   active case detection
ACPR  adequate clinical and parasitological response
ACT   artemisinin-based combination therapy
AL    artemether-lumefantrine
AMO   amodiaquine
API   annual parasite incidence
AusAID Australian Agency for International Development
CQ    chloroquine
DHA   dihydroartemisin
DHP/DHA-PPQ dihydroartemisinin-piperaquine
ERC   Ethics Review Committee
FSAT  Focal Screening and Treatment
G6PD  Glucose-6-Phosphate Dehydrogenase
GFATM Global Fund Against AIDS, Tuberculosis and Malaria
GF    Global Fund
GMP   Global Malaria Programme
GMS   Greater Mekong Subregion
GPARC Global Plan for Artemisinin-Resistance Containment
IPT   Intermittent preventive therapy
IPTi  Intermittent preventive therapy for infants
IPTp  Intermittent preventive therapy for pregnant women
IR    intra-rectal
IRD   Institutional Review Board
LLIN  long-lasting insecticidal net
MSAT  mass screening and treatment
NMCP  National Malaria Control Programme
Pf    *Plasmodium falciparum*
Pv    *Plasmodium vivax*
Pk    *Plasmodium knowlesi*
PCR   polymerase chain reaction
PNG   Papua New Guinea
PQ    primaquine
QA    quality assurance
RBM   Roll Back Malaria
RDT   rapid diagnostic test
RITM  Research Institute for Tropical Medicine
SEA   South-East Asia
SEARO WHO South-East Asia Regional Office
SOP   standard operating procedure
SP    sulfadoxine-pyrimethamine
TES   therapeutic efficacy studies
WHO   World Health Organization
WPRO WHO Western Pacific Regional Office
The second meeting of the Pacific Malaria Drug Resistance Monitoring Network was held in Manila, Philippines from 6 to 7 May 2013, two years after its official launch. The meeting was attended by three temporary advisers, two observers, 15 WHO Secretariat and 13 participants from seven countries: Indonesia, Malaysia, Papua New Guinea, Philippines, Solomon Islands, Timor-Leste and Vanuatu.

The objectives of the meeting were:

1) to assess the national malaria treatment policies and antimalarial drug efficacy data and monitoring systems, 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 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 presentations, technical presentations by the participants and WHO staff, and group discussions. All seven member countries since the last meeting have conducted or are about to conduct therapeutic efficacy studies (TES) and have plans for the next two years. The country representatives revisited their respective 2011 malaria drug efficacy monitoring plans and shared what has been accomplished to date, as well as the gaps and areas for improvement. The need for capacity building at all levels of TES implementation was highlighted. A number of common challenges were identified such as difficulty reaching adequate sample size in view of the decline in malaria patients, definition of sentinel sites, duration of recruitment, quality assurance for malaria microscopy, laboratory support for molecular analysis, migration and human resources.

There was group work for the development of country plans over the next two years. Planned activities include setting up or strengthening a quality assurance system for microscopy, continuation of ongoing TES and commencement of new studies in other sites. The exchange of information led to the revision and harmonization of country plans for 2013 to 2015. The TES activities for the next two years are largely funded by the Global Fund and AusAID, but sustainability is an issue.

It was assessed that the network founded two years ago contributed to the harmonization of the TES across the countries of the network. It was also concluded that the network, due to the recent availability of funding, is now ready to support country-level TES and conduct regional activities and effectively coordinate drug resistance monitoring in the region.

The current TES involves a variety of partners, but the network would profit from strengthening existing partnerships and establishing new ones. Given the emergence of the artemisinin resistance in the Greater Mekong Subregion, intensification of drug resistance monitoring throughout the region is essential.
Recommendations from the meeting were the following:

1) Ensure that the TES country plans are fully implemented to a high standard, following the WHO standard protocol including analysis of Day 3 positivity data (as an indicator for artemisinin resistance) as part of the TES. Priority should be given to first-line drugs;

2) The network with the funding now available should support countries to address identified gaps and needs in TES implementation;

3) The network should support regional- and country-level capacity building (including cross-country visits) in areas relevant to the implementation of TES;

4) The network should contribute to strengthening existing partnerships and facilitate the establishment of new ones, where needed. Partnerships should be built on common interest and mutual benefit and the agenda should be set together;

5) The network should facilitate the exchange of data and information at regional and country level;

6) The network should support independent monitoring of TES, quality assurance of microscopy and data validation as key regional activities;

7) The network should encourage and facilitate operational research that contributes to improved drug efficacy monitoring and prevention of artemisinin resistance;

8) The network and countries should be actively engaged in securing long-term funding;

9) The next network meeting should take place in one year in Malaysia.
1. INTRODUCTION

Access to early diagnosis and affordable, safe, prompt and effective antimalarial combination treatment for all at-risk populations is one of the strategies embodied in the Regional Action Plan for Malaria Control and Elimination in the Western Pacific (2010–2015). The emergence of resistance to antimalarial drugs thus poses a major public health challenge to the control and elimination of malaria in the Western Pacific Region, and also poses a serious threat at the global level.

The emergence of artemisinin resistance in the Greater Mekong Subregion (GMS) has garnered much attention and points to the necessity of intensified drug efficacy monitoring throughout the Region. Proper management of cases must be ensured, and changing patterns of resistance must be detected earlier on. A network responsible for monitoring drug efficacy in the Greater Mekong Subregion has been established. Complementing the GMS network, the Pacific Malaria Drug Resistance Monitoring Network was established in 2011 to strengthen the capacity of the region to prevent and address artemisinin resistance, coordinating therapeutic efficacy monitoring and informing programme decisions.

The Second Pacific Meeting served as the venue for taking stock of actions taken upon the recommendations presented at the conclusion of the First Pacific 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. This meeting in Manila brought together national malaria programme managers and focal persons on malaria treatment from seven countries: Indonesia, Malaysia, Papua New Guinea, Philippines, Solomon Islands, Timor-Leste and Vanuatu. It also brought together other stakeholders, partners and technical experts to explore collaboration and define the way forward. The WHO Regional Office for the Western Pacific and its partners, in collaboration with the WHO Regional Office for South-East Asia, organized the meeting. The meeting took place from 6 to 7 May 2013 in Manila, Philippines.

1.1 Meeting objectives

1) To assess the national malaria treatment policies and antimalarial drug efficacy data and monitoring systems, 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 develop the Pacific Malaria Drug Resistance Monitoring Network plan of action, including partner cooperation, resource mobilization and linkages with other networks.

1.2 Welcome remarks

Dr Eva Maria Christophel, Team Leader, Malaria and other Vectorborne and Parasitic Diseases, WHO Regional Office for the Western Pacific, welcomed all the attendees to the meeting and recounted how the Pacific Drug Resistance Monitoring Network was established in 2011 with seven member countries. She expressed enthusiasm at the prospect of hearing how far the network had come two years later.

1.3 Opening remarks

Dr Sergey Diorditsa, Team Leader, Expanded Program on Immunization, WHO Regional Office for the Western Pacific, delivered the opening remarks in behalf of Dr Shin Young-soo, WHO
Regional Director for the Western Pacific. He emphasized how the developing resistance to artemisinin and other antimalarial drugs demands the international community’s immediate attention. He recalled how in 2008, artemisinin resistance was confirmed on the Thai-Cambodian border, prompting containment efforts from the two countries which later extended to Myanmar. He highlighted the importance of a reliable monitoring system and how this must be prioritized for containment efforts to be successful. He cited the four drug resistance monitoring networks in the region, and expressed his optimism about the Pacific Malaria Drug Resistance Monitoring Network.

1.4 Nomination of Chair, Vice-Chairs and Rapporteur

Dr Eva Maria Christophel called for the nomination of Chairperson, Vice-chairperson and Rapporteur. Mr George Taleo, Malaria Programme Manager, Ministry of Health, Vanuatu was nominated as Chairperson. Dr Marti Kusumaningsih, Directorate General of Disease Control and Environmental Health, Sub-directorate of Malaria, Indonesia was nominated as Vice-Chair. Dr Raden Shamila binti Radin Hisham, Medical Research Specialist Officer of the Institute for Medical Research, Malaysia was nominated as Rapporteur.

2. PROCEEDINGS

2.1 Technical Session 1: Update on antimalarial drug efficacy monitoring and resistance

2.1.1 Global updates on tracking and mapping antimalarial drug efficacy

Ms Amy Barrette, from the Drug Resistance and Containment Unit of the Global Malaria Programme, WHO Headquarters, presented an update on the tracking and mapping of antimalarial drug efficacy. She started by presenting the data sources of her updates: published data found in scientific literature, unpublished reports and raw data, all of which are found in the WHO global antimalarial drug resistance database. From 2005 to 2012, a total of 325 studies in 38 countries were conducted on antimalarial drug efficacy all over the world. In the Western Pacific Region alone, 27 were conducted in Cambodia, four in China, eight in Lao People’s Democratic Republic, five in the Philippines and one in Solomon Islands. She also presented the number of cases of drug resistance in the region from 2005 to 2012 according to the type of ACT drug, citing that most drug-resistant cases were those treated by artesunate-lumefantrine (15 cases) and dihydroartemisinin-piperaquine (15 cases).

In terms of data reported, three sources were used: global reports, crystal reports and maps. Global reports used as references for her presentation were the (1) Susceptibility of Plasmodium falciparum to antimalarial drugs: report on global monitoring 1996–2004 which was published in 2005, and (2) Global Report on Antimalarial Drug Efficacy and Drug Resistance, 2001–2010 published in 2010. She presented the countries in which dihydroartemisinin-piperaquine was used as a first- or second-line treatment and later presented the treatment failure rates associated with such drug by subregion. Of all the countries using the drug, Rwanda had the highest treatment failure rate at >10% from 2001 to 2008. In the Western Pacific countries, specifically in Cambodia, treatment with artemether-lumefantrine has had the highest range of treatment failure rates, while quinine-tetracycline had the lowest range. In China, the highest range of treatment failure rate was with chloroquine, while the lowest range was with artemether-lumefantrine and artesunate suppository 7-day treatment. These data are based on 2001–2010 reports. Data were also presented including the most recent 2013 reports, and among the Western Pacific Region countries, Cambodia still tops the list in terms of treatment failure rates (associated with artemether-lumefantrine, artesunate-mefloquine and dihydroartemisinin-piperaquine).
Using maps, Ms Barrette showed the geographical presentation of TES data (2005–2011) as registered in the GMP website, representing a total of 152 sentinel sites for TES all over the world. She also showed how the maps can be customized (for learning purposes) by treatment, study outcome indicator (percentage of patients positive on Day 3, percentage of patients with treatment failure), geographic area (study site, country, WHO region) and time. Multiple sites can also be selected to compare over time, all regions can be selected for a global overview, and data can be exported to an Excel sheet for further analysis and comparison.

2.1.2 Updates on antimalarial drug resistance in the Western Pacific Region and progress with the Pacific Monitoring Network

Dr Eva Christophel presented the updates and the actions taken since the recommendations from the 1st Pacific Network Meeting conducted in August 2011. Follow-up actions to date include: (1) the establishment of the Pacific Malaria Drug Resistance Monitoring Network in 2011; (2) the recruitment of a coordinator by mid-2013, with a tenure of three years, and (3) mobilization of the funding for the core activities of the Pacific Network from the Bill and Melinda Gates Foundation by the end of 2012, as part of the Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion. However, no action has yet been taken with regard to the following: (1) finalization and endorsement of the two-year draft national drug efficacy monitoring plans by country; (2) identification of capacity building and technical assistance needs and assistance sought from the network; (3) adherence to the latest WHO protocol for antimalarial drug efficacy monitoring and (4) regular review of country data (including data on Day 3 positivity as an early warning sign of emerging artemisinin resistance) and sharing within the network. The lack of follow-up has been due to inadequate funding and human resources.

Dr Christophel also presented updates on developments in malaria and in summary, she noted that there has been a tremendous progress in reducing malaria in the region. Malaria drug resistance (Pf and Pv) has been a reality since the 1960s, but TES has enabled detection of resistant cases and the ensuing revision of national treatment regimens. However, countries should still be cautious as the emergence of artemisinin-resistance has been detected and confirmed in Cambodia in 2008. As of now, four GMS counties are affected, with containment operations ongoing. She urged the members to be aware that risk factors for artemisinin resistance exist in some countries, particularly the availability and use of oral artemisinin monotherapies.

Dr Christophel also cited unprecedented political commitment to malaria, as evidenced by the recent international meetings held in support to malaria control and elimination and combating malaria drug resistance. With funds available, the Pacific Malaria Drug Resistance Monitoring Network can already start to support intensified high-quality drug resistance monitoring for the purpose of informing malaria policies. With this, she presented the terms of reference of the network, to clearly specify its roles and responsibilities in relation to such a monitoring initiative.

2.1.3 Update on antimalarial drug resistance in the South-East Asian Region

Dr Anand Joshi, WHO-SEARO presented drug efficacy monitoring updates from the South-East Asia Region. He began by presenting the malaria profile in the Region as of 2011, by country. Referencing data from 2000 to 2011, the overall peak of cases in South-East Asia occurred in 2001 (at around 2.8 million cases), while the peak of deaths also occurred in the same year (at around 6500). In terms of malaria incidence (API per 1000 population) in the SEA Region in 2011, Sri Lanka had the lowest API (0.12 per 1000) while Timor-Leste had the highest (17.18 per 1000). Malaria mortality rate was lowest in Sri Lanka (0.00 per 100 000), Democratic People’s Republic of Korea (0.00) and Nepal (0.01) while Myanmar had the highest mortality rate (2.01). In terms of the distribution of confirmed malaria deaths across the Region within the same period, India had the greatest share at 41.4% while Nepal and Bhutan had the lowest at 0.1%. Overall, there has been a downward trend in terms of API, mortality and case fatality rates from 1994 to 2011 with minimal
fluctuations in between. There was an increase in API from 2007 to 2009, but a subsequent decrease in 2010 and 2011. Dr Joshi also noted that the increasing distribution of ACTs from 2004 to 2011 was consistent with the plummeting number malaria deaths within the same period.

Dr Joshi went on to discuss briefly the situations in each of the SEA countries. Overall, the efficacy rates of artemisinin in all countries have reached 100%. Artemisinin resistance prevention in the Region is focused on: (1) improving access to diagnostics and artemisinin-based combination therapy; (2) increasing monitoring and surveillance to evaluate the threat of artemisinin-resistance and (3) strengthening networking to mobilize resources.

Dr Joshi concluded his presentation with the plans and next steps to be taken and expected challenges. Next steps include: (1) quality assurance for the drug; (2) expansion of quality and early case-finding and treatment; (3) exit strategy to allocate more internal funding; (4) strengthening of the artemisinin-resistance containment network, and (5) implementation of antimalarial drug efficacy monitoring. He also presented challenges such as preventing the emergence and spread of artemisinin resistance, addressing fake/counterfeit drugs, monotherapy and irrational use of drugs, difficulty in the screening of imported cases, introduction of \textit{P. malariae} and \textit{P. knowlesi}, strengthening surveillance and monitoring, the improvement of multisectoral and cross-border collaboration, and sustaining political support, funding and community participation.

2.1.4 The role of country networks in antimalarial drug efficacy monitoring and prevention of drug resistance

Dr Dorina Bustos, Malaria Technical Officer, WHO-Mekong Malaria Programme, Office of the WHO Representative to Thailand, presented on the importance of country networks in monitoring antimalarial drug efficacy and the prevention of drug resistance. She first provided an overview of the support that WHO extends to countries in the Greater Mekong Subregion. This has contributed to the Mekong malaria map shrinking to concentrate on the borders, where delayed parasite clearance despite artemisinin-based combination therapy was noted in 2012. Sentinel sites for drug efficacy monitoring have been maintained in the GMS, with expansion to new sites in 2012 to 2013 for continued monitoring.

Lessons learnt from the Mekong countries include the challenge that quality control procedures, the main concern overall, are not routinely observed by the national programmes (unlike the research institutions), but this can be remedied in due course with capacity strengthening, practice and constant supervision. WHO technical support, monitoring visits and validation of results (slides, PCR, data entry) were also found to be very useful. Biannual meetings with principal investigators and NMCPs for information/data-sharing resolve common issues and facilitate planning for future studies.

Lastly, Dr Bustos emphasized that the role of the Mekong network in the Pacific malaria drug resistance monitoring efforts will be to bridge the two WHO regions and the Mekong WRs, identify the gaps contributing to the regional malaria challenges alongside the partners, document good practices/publications and raise funds through liaison with development partners.

2.1.5 Overview of emergency response to artemisinin resistance in the GMS

Dr Christophel started by presenting the specific areas in Cambodia from 2001 to 2011 that have seen increasing Day 3 parasite positivity rates after treatment with an artemisinin-based combination therapy. She further explained that the efficacy of ACT as a clinical and parasitological cure is not compromised as long as the partner drug in the combination is working. In terms of clinical outcomes, fever clearance time may be prolonged which can lead to dissatisfied patients.

The suspected foci of artemisinin resistance as of 2013 is noted to be within the border areas of Cambodia, Thailand, Viet Nam and Myanmar.
Dr Christophel zeroed in on the action pillars of the Global Plan for Artemisinin Resistance Containment (GPARC), which is intended to address the problem of artemisinin resistance. Based on the GPARC, areas are being classified as Tier I, II or III depending on the presence or absence of credible evidence showing artemisinin resistance, and whether there is a significant influx of people to and from areas shown to have artemisinin resistance. Each tier classification has its own corresponding WHO-recommended action to contain, eliminate or prevent resistance.

The zoning for malaria containment within Thailand and Cambodia was shown. Interventions pertinent to malaria containment were (1) focused diagnosis and treatment, (2) training and recruitment of 3000 village malaria workers and mobile malaria workers to implement the interventions, (3) mapping of malaria incidence in Cambodia, (4) encouragement of community engagement and (5) enforcement of the ban on artemisinin monotherapy. Areas within Myanmar, Thailand, Cambodia and Viet Nam with ongoing containment activities were cited.

The response to artemisinin resistance in the GMS was assessed. The findings mainly show that the approach outlined in the GPARC and several associated national strategies and plans were appropriate. However, it was also found that much has yet to be done, particularly in terms of intensity, coverage and quality. In response to the assessment findings, the emergency response framework was devised with identification of its purpose, focus and 15 priority actions in four areas.

The last part of the discussion focused on WHO’s establishment of a regional hub for coordination and support for artemisinin-resistance containment within the region. Key activities were discussed, with a target to secure financial support (US$ 100 million) from the Global Fund in support of the regional artemisinin resistance initiative. The concept note would be developed by the end of July 2013. As of time of writing, discussions are ongoing regarding the Principal Recipient and governance mechanism.

2.1.6 Discussion

On the query about which geographical area poses a bigger threat in terms of the emergence of drug resistance, the situation in Western Cambodia was worsening every year, according to Dr Bustos. She also cited the decreasing adequate clinical and parasitological response (ACPR) of Thailand’s current first-line ACT (artesunate mefloquine) and the particularly low ACPR of 75% on the Thai-Myanmar border.

Regarding the possibility of harmonizing the subregional treatment policy across the different countries, Dr Bustos affirmed that this recommendation was raised years ago but she also clarified that WHO can only make recommendations. The final decision to act is still made by the countries.

There was a good exchange on the likelihood that there is selection for resistant cases in the face of significant decline in malaria incidence and increasing drug resistance. Dr Bustos pointed out that it is in containment areas where the full package of interventions to reduce malaria has been implemented, resulting in the near disappearance of falciparum malaria – and these cases were the ones found positive on Day 3.

Another issue discussed was G6PD deficiency in Indonesia. The national programme of Indonesia will strengthen diagnosis, validation, treatment and the quality of its services along with scaling up of interventions. The acceptability of prophylaxis was raised, particularly in areas where access to services is difficult. An example of this is in Papua New Guinea.

Monitoring of drugs used in the practice of intermittent preventive therapy was emphasized, in addition to routine drug efficacy monitoring.
2.1.7 Summary

There has been success in the malaria programmes both in the Western Pacific Region and the South-East Asia Region. In the Western Pacific Region, there has been significant decline in malaria incidence and mortality, with some countries/areas progressing to elimination. In South-East Asia, Sri Lanka is on track for elimination but there are still three countries with high levels of incidence and mortality rates.

There remain many challenges, the most serious of which is the emergence of drug resistance. In the Western Pacific Region, ACTs have been efficacious but early warning signs of ACT failure have emerged. In South-East Asia, artemisinin resistance has been noted in Myanmar. ACT use has been satisfactory in most countries but there is a call for strengthened surveillance and monitoring of efficacy of ACT and resistance both to artemisinin and partner drugs.

The TES data is incorporated into the WHO database, which is quite comprehensive with an interactive map that shows the drugs in use and their efficacy in each site. This provides a view of the global efficacy status of antimalarial drugs.

The Western Pacific Region has fewer data spots than the other regions, which points to the importance of TES surveillance in the Region in order to obtain more data not just to fill in the map but also to inform the countries so they can update their treatment policies.

The presentation of the Great Mekong Subregion network clarified its role in helping intensify surveillance and monitoring. There was a good discussion on extended protocols between countries, use of single standard protocol for Pf and Pv, TES throughout the subregion, and the manner by which funding is secured. These are better achieved through the synergy of a network than by single countries. The network facilitates cross-border collaboration, especially cross-border containment programs.

It is important to regularly conduct TES in the regions along with the incorporation of the Day 3 parasite positivity rate to monitor the early emergence of artemisinin resistance. TES also demonstrates the efficacy of companion drugs, which further underscores its importance.

The Greater Mekong Subregion artemisinin resistance containment programme and the comprehensive emergency response programme will help the Pacific region to combat and contain resistance should the situation escalate to the same level.

2.2 Technical Session 2: Country updates on the malaria situation, treatment policy, drug resistance and monitoring, and technical issues

2.2.1 Papua New Guinea

Professor Peter Siba, Director of the Papua New Guinea Institute of Medical Research (IMR) presented data on the monitoring of artemether-lumefantrine (first-line) and dihydroartemisinin/piperaquine (Eurartesim) (second-line) in specific areas such as in Madang, Maprik and Alotau. Recent results from Madang indicate that PCR-corrected ACPR in Pf and Pv patients were higher than in 2007. IC50 values for DHA-piperaquine and primaquine had increased between 2006 and 2012. Enrolments in Alotau and Maprik (Global Fund-sponsored DR monitoring) are still ongoing. Ongoing studies include: (1) Safety, tolerability and pilot efficacy of short-course, high-dose PQ treatment for liver stages of Plasmodium infection; (2) Artemisinin-naphthoquine compared to AL combination therapies in children with uncomplicated malaria; and (3) Pharmacokinetics of piperaquine in pregnancy. Operational research includes: (1) Evaluation of effect of LLIN; (2) Evaluation of treatment policy implementation (country-wide surveys); (3) LLIN insecticide resistance monitoring; and (4) Assessment of insecticide-treated plastic sheeting for vector
control. These studies have been carried out through the collaboration of IMR with the Ministry of Health.

Points clarified during the discussion included: (1) Enrolment is still ongoing for the study on piperazine so there is still no data available; results of the monitoring of AL (as part of the Global Fund program) are pending as patient enrolment is still ongoing; (2) There are two types of studies ongoing in PNG—one is the clinical trials that are part of the collaboration between IMR and their overseas collaborators, such as the standard treatment trial published on a study in 2004 (Karunajeewa et al. 2008). The other type is purely efficacy studies under the Global Fund Round 8 grant. There was a delay in the start of these studies because of a delay in the rollout of the new treatment policy with first-line treatment AL. It was considered irrational to repeat the same study twice in two years before the drugs had been actually rolled out; (3) Dr Hetzel also pointed out that the decline in cases shown in the earlier presentation of Dr Christophel can be attributed purely to the large-scale distribution of bednets, because at that time there was no change in treatment policy. He said that the additional effect of the large-scale roll-out of ACTs will only be seen in the future.

2.2.2 Solomon Islands

Dr Lyndes Wini of Solomon Islands presented a summary of the malaria trends in the country from 2000 to 2012, showing significant reductions. The current national malaria treatment policy in place since 2008 stipulates the use of AL for uncomplicated *P. falciparum* malaria and AL + PQ used for uncomplicated *P. vivax* malaria. Artesunate suppositories and artesunate injections are used for severe malaria. Weekly chloroquine prophylaxis is recommended for pregnant women. He gave a brief overview of the antimalarial drug efficacy situation and recent changes in malaria treatment policy. In 2001, the efficacy of chloroquine dropped as low as 33% which resulted in the shift from chloroquine monotherapy to chloroquine plus sulfadoxine-pyrimethamine. In 2005, TES showed 88% ACPR to CQ and SP. In 2008, AL was adopted for both vivax and falciparum.

Results of the TES done in 2008 at Auki in Malaita province yielded 100% efficacy of AL for both falciparum and vivax, although the sample size was quite small at 54 and 35, respectively. The most recent TES on AL at Tetere in Guadalcanal province (initiated in 2011 and planned to complete by June 2013) has so far shown an ACPR (without PCR-correction) of 91% on Day 28 for falciparum (with 22 patients enrolled) and 94.9% for vivax (with 69 patients enrolled). The WHO 28-day protocol was used for both *Pf* and *Pv*. Recruitment has been slow for the most recent study (2011–2013) because of the decreasing malaria prevalence since 2000.

There was no formal publication for sharing of the results yet, and PCR genotyping results were still awaited. Dr Wini said they would like to collaborate with the Australian Army Institute and other colleagues to formalize the findings.

He cited that there was now better coordination for the TES studies but that the changing epidemiology has affected recruitment rates at sentinel sites, particularly for the falciparum arm. More vivax cases are now reported. Human resources remain an issue in the face of competing activities of the staff. There is also no dedicated research institute to conduct these operational studies, and the team operates out of an office without laboratory facilities.

He pointed out that they are encouraged by the presence of the Pacific Malaria Drug Resistance Monitoring Network which provides for improved collaborative efforts between member countries.

Dr Wini also presented the different operational studies and their status. The Malaria Indicator Survey (MIS) completed in 2011 showed a point prevalence of malaria of less than 0.5% across the country.
They are also planning to conduct a primaquine safety and efficacy study similar to that ongoing in Vanuatu, exploring both the low dose and high dose of PQ. Another MIS and TES are being planned for in 2014. Solomon Islands is also considering a G6PD prevalence study in 2014, exploring the possibility of piggy-backing to the MIS. Dr Wini pointed out that the G6PD issue is not settled and there is residual reluctance among physicians to prescribe PQ. Currently, the recommended dosage of PQ remains at the 0.25kg/kg dose if the patient’s G6PD status is unknown.

Dr Wini also reported that vector control activities resulted in high LLIN coverage (about 91%) and that diagnostic coverage is quite high with the introduction of RDTs. He concluded his discussion with the point that the primary need is to strengthen collaboration between low technically resourced countries and partner institutions in the region. He said this in reference to the lack of laboratory capacity and technical expertise for research in Solomon Islands, which he was optimistic would be addressed through the network.

The following points were cited during the discussion: (1) The need to take caution in the use of the term “failure”, particularly in reference to the efficacy study for vivax. It was pointed out that it may not be an issue of treatment failure but more of the short half-life of AL. The samples were not PCR-corrected but confirmed through microscopy results, as observed on Day 21/28. This could mean that it is very sensitive and there is a possibility of reinfection/relapse on Day 28. There is a need to think about better terminology to distinguish it from failure; (2) The protocol recommends reporting the Day 28 results and then 42 day results; (3) The planned two-year study should be considered before proceeding. It was agreed that the afternoon session would discuss whether it is it is worthwhile to continue with the small sample size of 50.

2.2.3 Vanuatu

Mr George Taleo, Malaria Programme Manager, Ministry of Health, Vanuatu, presented the malaria trends in the country from 2000 to 2012, and showed API figures (as of 2012) as indication of transmission in the different areas. Changes in drug efficacy and treatment policy over time were noted, dating back to the 1980s. The current national malaria treatment policy used is AL for *P. falciparum* and *P. vivax* and primaquine for *P. vivax* while artesunate injection is used for severe malaria.

The results of the TES conducted over a one-year period (March 2011 to April 2012) indicate ACPR to AL (for *P. vivax* infections) in 79 out of 80 patients enrolled (98.8%). One patient was positive on Day 28. Unfortunately, the blood sample for the patient was too small to do genotyping so it was not determined whether it was a recrudescence, relapse or reinfection. This is a concern for cases which show failure or relapse. The importance of obtaining better blood samples was emphasized.

No *Pf* patients were recruited during the study period. There is an ongoing TES for AL (for *P. falciparum*) in Luganville, Sanma Province, which commenced in May 2013 and will end in April 2014, run in parallel with a clinical study of the efficacy and safety of primaquine for *P. vivax*.

Issues and bottlenecks encountered were the absence of a medical research institution, the limited country capacity for TES and the decreasing number of cases. Mr Taleo also pointed out the need to prioritize the focus of the operational research either on case management or vector control. Recommendations include collaboration with research institutes abroad, formulation of PCR support from Australian Army Malaria Institute in Brisbane, and the Pacific Network helping out in supporting capacity-building, setting laboratory support for QA and PCR and collaboration on operational research. Planned operational research activities include (1) primaquine on *P. vivax* relapses and (2) performance of Care Start RDTs for passive case detection, reactive case detection and prevalence surveys.
During the discussion, the importance of building capacity was raised and how the network and other similar networks in the region like the APMEN could be tapped to provide assistance. Mr Taleo pointed out that the programme needs to identify people for training as focal points who are willing and committed to delivery.

2.2.4 Philippines

Dr Fe Esperanza Espino, Head, Research Institute for Tropical Medicine of the Philippines, presented the malaria trends from 2000 to 2012, which showed a consistent downward trend since 2005. Detailing the TES conducted, TES for CQ and SP (for *P. falciparum*) conducted from 2001 to 2002, and from 2003 to 2007 showed a treatment failure rate of 10 to 20% for Palawan and other sites in selected Mindanao provinces (located in the southern Philippines), and less than 10% in sentinel sites in northern Luzon provinces. TES results for CQ for *P. vivax* conducted in 2005 showed no recurrence of parasitemia. TES for CQ and PQ (for *P. vivax*) from 2009 to 2012 resulted in 0.8% and 17.9% recurrence of parasitemia, respectively.

These results formed the basis for the changes in the treatment guidelines. The current first-line treatment for *P. falciparum* is AL, the second-line treatment is oral quinine, while for severe cases, quinine plus AL are used, along with artesunate suppository as a pre-referral treatment. Treatment for *P. vivax* remains the same with chloroquine and primaquine.

Challenges identified in the TES implementation include timeliness in securing funding for molecular assays, institutional reviews, a decreasing number of malaria cases (the limited sites and remoteness of area affect recruitment and follow-up security), dedicated TES team (subnational or in sentinel sites), anti-relapse efficacy of higher doses of primaquine in G6PD deficiency cases, and treatment for probable failure in pregnancy. Ongoing operational research involving malaria case management includes studies on (1) fluorescent in-situ hybridization, (2) planned phase III tafenoquine trial and (3) G6PD deficiency tests.

2.2.5 Malaysia

Dr Mohd Hafizi, Principal Assistant Director, Disease Control Division of the Ministry of Health, Malaysia, presented the malaria trends in the country from 1961 to 2012, characterized by a consistent downward trend since 1995. There were a total of 4725 cases (all species) as of 2012, with 16 deaths and a 0.34% case fatality rate.

The national treatment guidelines were developed in 1994 and reprinted in 2000. Revision is currently underway with an expected completion date of June 2013. For uncomplicated chloroquine-sensitive *P. falciparum* infections, the treatment is chloroquine and primaquine while for uncomplicated chloroquine-resistant *Pf* infections (for both outpatient and in-patient malaria cases), sulfadoxine-pyrimethamine and primaquine are given. The proposed revised guidelines will have AL or artesunate-mefloquine as first-line choice for uncomplicated *Pf*, with an alternative of oral quinine and doxycycline. Second-line drugs will be AL plus doxycycline. Artesunate (IV) and doxycycline would be used for severe *Pf* infections, with quinine and doxycycline as the alternative. Chloroquine and primaquine will continue to be used for *P. vivax* and *P. ovale* infections. Second-line would be AL and primaquine. Treatment for *P. malariae* and *knowlesi* is the same as that for *Pf*.

Studies on the status of *Pf* resistance to antimalarial drugs were also presented. The study of Cox-Singh et al. done in Sarawak from 1999 to 2000 yielded a 43% failure rate to the CQ and SP combination. The study done in Terengganu and Perak in 2000 and 2001 showed 51.4% and 62.5% failure rates, respectively. The national anti-malaria drug response surveillance programme implemented across 18 sites in seven endemic districts in Sabah from 2003 to 2006 resulted in a 23.9% early failure rate to CQ, a 6.8% late failure rate to CQ (among 117 cases), a 4.2% early failure rate to CQ+SP and a 1.8% late failure rate to CQ+SP (among 167 cases).
These studies did not comply with the WHO recommended protocol. Facilitators (from yesterday’s session) suggested that another round of TES be conducted to guide change in the national malaria drug policy. The drugs to be tested are AL for *Pf* and *Pk* and CQ and PQ for *Pv*, with sentinel sites being limited to two states – Sabah and Sarawak.

*Pk* cases are on the rise in Malaysia, so the drugs for this species will also be included in the TES. Potential problems cited were the difficulty in road access, lack of laboratory facility in the sentinel sites and the rapid turnover of staff. In terms of resources and funding, Dr Hafizi said that Malaysia is fortunate to have been able to fund TES activities but that they also welcome external support, not only financial but also technical expertise for TES.

### 2.2.6 Indonesia

Dr Marti Kusumaningsih, from the Sub-directorate of Malaria, Directorate General of Disease Control and Environmental Health, Ministry of Health, presented the status of malaria in Indonesia. Epidemiological data were presented and as of 2011, there were an estimated 1 411 156 malaria cases (all species), 1151 malaria deaths and 935 648 unconfirmed cases. Cases of chloroquine resistance and multiple drug resistance (1978–2003) were mapped out, as well as the efficacy of CQ and SP in Indonesia (1998–2003). Use of ACTs, specifically artesunate-amodiaquine, for uncomplicated *P. falciparum*, and artesunate injection for severe malaria cases, started in 2004 as a result of poor efficacy results observed for CQ and SP. Dihydroartemisinin-piperaquine (DHP) was later adopted for use in Papua and West Papua in 2008. TES has been done for artesunate, amodiaquine and DHP in selected sites in the provinces of Samarinda, Tomohon, Jayapura, Timika, East Sumba and West Sumba from 2005 to 2010 but the results were not available for the presentation.

Also discussed were the artemisinin resistance prevention campaign in Indonesia. The objectives include (1) improving the access to diagnostics and artemisinin-based combined therapy; (2) increasing monitoring and surveillance to evaluate the threat of artemisinin resistance; and (3) strengthening networking to mobilize resources. The next steps are to implement quality assurance for the antimalarial drugs used, expand quality and early case-finding and treatment, implement an exit strategy involving allocation of more internal funding, and develop an artemisinin resistance containment network and antimalarial drug efficacy monitoring.

The objectives and activities of the malaria elimination programme were also discussed. Overall, malaria poses a huge burden and challenge to Indonesia, making its control and elimination a national priority. The thrusts of the programme include improvement of service quality and community access to health services, expansion of networking with stakeholders and establishment of sustainability measures for the programme.

### 2.2.7 Timor-Leste

Dr Maria do Rosario de Fatima Mota began with the summary of malaria trends in the country, from 2002 to 2012, using incidence per 1000 population. The current national treatment for uncomplicated *P. falciparum* malaria is artemether-lumefantrine (first-line treatment), followed by quinine and doxycycline (second-line treatment). Chloroquine and primaquine are used as first-line treatment for *P. vivax*.

TES conducted in 13 sentinel sites distributed across eight districts in 2011 to 2012 showed 17.5% positivity for Day 28 with CQ (for *P. vivax*), and zero positivity for Day 42 with artemether-lumefantrine. The TES results were shared through reports and publications.

Issues identified pertain to (1) problem areas preventing the routine national TES implementation; (2) the high dropout rate of patients; (3) the fact that patients do not like to
participate; (4) capacity of medical laboratory analysts; and (5) lack of funds after 2014. Cross-border collaboration and support to carry out PCR were some of the suggestions offered.

Dr Mota also enumerated Indonesia’s expectations of the Pacific network: (1) mitigation of the emergence of drug resistance by information-sharing among the countries; (2) improvement of knowledge and skills related to TES; and (3) coordination with the other research institutes and international organizations toward improvement of TES.

A number of operational research activities were recently completed and these included (1) Quality control of RDT kits; (2) Health facility survey – 2010; (3) Malaria Indicator Survey – 2010. Planned and ongoing operational research includes G6PD deficiency prevalence in Timor-Leste, Health Facility Survey 2012 and Malaria Indicator Survey 2013.

2.2.8 Summary

All countries in the network have been working hard to implement the plans developed in 2011, although technical and financial issues have hindered their complete realization. There was interesting background information on the process of shifting to ACTs and how the TES results influenced changes in drug policy in some countries, while in others they were not used to guide the drug of choice. Some countries do not have sufficient data to document resistance and just shifted to ACT by default. Malaysia was the latest country to make this move this year. Four countries also mentioned that they are still using chloroquine for *P. vivax*. One area in Indonesia still uses amodiaquine as the partner drug for ACT.

The presentations focused on routine TES studies which supported the policy shift towards ACTs. Proper monitoring of ACTs and continuous training of staff were cited as very important. The countries also reported monitoring of chloroquine resistance to *P. vivax*.

The lack of capacity of countries to do PCR parasite genotyping was a common issue raised. It was assessed that establishing in-country PCR may not be feasible. It was recommended that a dedicated facility at the regional level be built for this purpose.

2.3 Technical Session 3: Update on technical issues to strengthen drug resistance monitoring

2.3.1 Update on methods for antimalarial drug resistance monitoring and use of the WHO standard protocol, practical issues, sentinel site selection, frequency of studies, data analysis and reporting of results

Dr Dorin Bustos, WHO Thailand presented updates on the methods to ensure quality in Therapeutic Efficacy Studies (TES). An introduction was first given about malaria multidrug resistance monitoring through TES. This was followed by discussions on the WHO standard protocols, microscopy quality assurance and quality data management and monitoring. Dr Bustos emphasized that of equal importance is meeting the requirements of the WHO Ethics Review Committee in order for the TES to be conducted.

Technical and administrative challenges were pointed out in assuring the quality of TES implementation. Among these are the study protocol itself, the treatment drugs used, sample size, frequency of studies, laboratory challenges (e.g. microscopy, finger-prick filter paper samples for polymerase chain reaction, CQ blood level assays for *P. vivax*), ethical considerations, clinical trial registration, data management, technical report writing and development of peer-reviewed publications.

Dr Bustos shared the observations and lessons learnt from Mekong countries in terms of assuring the quality of TES. These included: (1) quality control procedures in general which are not routinely observed by national programmes (as compared to research institutions), but can be
achieved with practice and constant supervision in due course; (2) monitoring visits with WHO technical support and validation of results which were very useful; (3) biannual meetings with principal investigators and NMCPs for information-sharing, resolving issues and planning for future studies; (4) suggestions for regular cross-border meetings between countries; (5) maintenance of sentinel sites; (6) TES as priority regular activity of NMCPs; (7) training workshops; (8) quality control of drugs; (9) data and slide validation and (10) timely data analysis.

2.3.2 Update on laboratory methods for monitoring malaria drug resistance

Dr Qin Cheng, Head of the Drug Resistance and Diagnostics of the Army Malaria Institute (AMI) in Brisbane, Australia, presented the different updates on laboratory methods for monitoring malaria drug resistance. There were four laboratory methods discussed, namely TES, in vitro susceptibility, molecular markers and drug concentration studies. The nature of the laboratory methods, plus their benefits, applications and limitations were discussed.

TES involve treatment of symptomatic patients with a standard dose of an antimalarial drug and subsequent follow-up of parasitemia and clinical signs and symptoms over a defined period. PCR is done to confirm species for Day 0 and day of failure (as a means of quality control for microscopy). Genotyping is intended to improve assessment accuracy. Day 0 samples are taken to understand parasite population diversity, and day of failure samples are taken to distinguish recrudescence from new infections. Genotyping is done to monitor changes in transmission. She compared the genotyping markers for \textit{P. falciparum} and \textit{P. vivax}, with those for falciparum (antigen), yielding more precise results than those for vivax. The estimate cost of reagents and labor is A$ 80 per subject.

She enumerated the different models for PCR and genotyping. TES teams that have PCR capability should focus on quality assurance. Those without PCR capability can collaborate with a research institute, citing AMI as a provider of PCR and genotyping support to Solomon Islands, Vanuatu and Timor-Leste. Staff of established laboratories can also be trained so PCR can be established locally.

The in vitro susceptibility test is the cultivation of malaria parasites in vitro with a range of antimalarial drug concentrations and measurement of inhibition of parasite growth. Dr Cheng emphasized that the standard in vitro susceptibility tests still need to be conducted to monitor drug resistance to companion drugs, detect changes in drug resistance profile in one location over time, compare drug resistance between locations, and detect ACT resistance when it is fully developed. She also showed the Minimum Inhibition Concentration levels for the different antimalarial drugs. In vitro susceptibility test for antimalarial drugs for \textit{P. falciparum} requires venous blood, a relatively high level of parasitemia (1000–80 000p/µL), a single strain infection, and setting up of cultures within six hours of blood collection. Quality control of plates and drugs was also emphasized. Limitations include the difficulty in assessing fixed-dose combinations, the requirement for a laboratory and a well-trained technician, and the inability to detect change to ART in samples showing delayed parasite clearance. Resistance thresholds are validated for chloroquine, quinine, mefloquine, amodiaquine and halofantrine, but not for artesunate, piperaquine and pyronaridine, among others.

Dr Cheng also cited the in vitro susceptibility test conducted in Cambodia which failed to detect artemisinin resistance. She explained that this was due to the fact that the ring stage of the parasite had not yet fully developed resistance to the drugs and this was not picked up by the standard in vitro test. She mentioned that the Ring Survival Assay, a new in vitro assay, should be conducted in conjunction with the standard in vitro susceptibility test where possible.

\textit{P. vivax}, on the other hand, is difficult to culture in vitro. There is differential susceptibility to antimalarial drugs at different developmental stages. There are also more procedures and repeatability is difficult. Resistance thresholds are not yet validated.
Molecular markers are used to detect genetic markers that modify drug target (enzymes) or drug transporter functions or affinities. Molecular markers are useful for large-scale community-level screening and surveillance such as prevalence distribution and change of mutations. The method is particularly useful for areas that have insufficient numbers of patients due to decreasing transmission. Samples can also be stored for future use. The use of molecular markers also has its limitations. Markers are only available for a limited number of drugs. Specifically, there is no marker yet for artemisinin resistance. Correlation with efficacy is not fully established and the use of markers requires laboratory and trained personnel.

Drug concentration measurement is another method which measures antimalarial drug and/or active metabolite(s) in whole blood, plasma or serum. Benefits of this method include accurate definition of true drug resistance, the fact that multiple tests can be performed with a single blood sample, and that several drugs can be assayed simultaneously. Samples on filter paper are easily obtained, transported and stored. The method also provides quantitative results and can potentially be used on non-invasive urine or saliva specimens. Dr Cheng also pointed out the method's limitations such as the training requirements and expensive equipment and supplies. Filter paper sampling is not possible for all antimalarial drugs (particularly artemisinins). There is also a lack of standardized methods and interpretation requires accurate dosing history and record of timing of sample collection.

Dr Cheng discussed details of the recommended sampling scheme and procedures for TES. She also explained the interpretation of genotyping results with three marker genes.

She then summarized the features of the different methods and how these can be applied to monitoring efficacy of ACTs. TES provides direct evidence on efficacy of ACTs while the in vitro susceptibility test monitors resistance to companion drugs and advanced ART resistance, establishes baseline and detects changes in a location. New assays are being developed to detect ART resistance phenotype. Molecular markers monitor resistance to some companion drugs. No markers are available for ART resistance, but a number of candidates have been identified. Drug concentration measurement facilitates the definition of true resistance.

2.4 Group Work: Development of Country Malaria Drug Resistance Monitoring Plans

2.4.1 Group 1: Pacific region

Papua New Guinea

TES sites for Papua New Guinea are Alotau and Maprik, with the parasite species for testing being *P. falciparum* and *P. vivax* on artemether-lumefantrine (first-line) and dihydroartemisinin-piperaquine (second-line) treatment. The budget (which was not indicated in the country plan presented) for this will be obtained through GFATM support until October 2014. Funding is needed especially for microscopy capacity building, in particular for the annual two- to three-week microscopy training to upgrade the microscopists at the IMR. Support is also required for the continuation of the annual competency assessment. The latter was provided by AMI for the last several years but it is better if the activity is funded internally. The country also needs support for an external study monitor and funding for dissemination of results.

Solomon Islands

Current TES sites for the Solomon Islands are Tere and Auki, Malaita, with *P. falciparum* and *P. vivax* to be tested on artemether-lumefantrine. Consistent with the recommendation during the meeting, it was decided to terminate the study in these sites as these have been ongoing for too long already. It was recommended that a new project be started in different sites – Munda (Western Province) and Kira Kira (Makira Province). The same species will be tested with artemether-lumefantrine, using the proposed budget through GFATM until December 2014 (USD 24,000).
External competency assessment and refresher courses for microscopy will also be conducted. Internal monitoring is proposed to be done on a monthly basis with monitoring by an external team every six months. Other needs/gaps identified were human resources, means of transport, equipment, training, and funding for equipment and transport.

Vanuatu

The TES site in Vanuatu will be at Santo, where artemether-lumefantrine will be used for *P. falciparum* and *P. vivax*, through proposed budget from GFATM and AusAID amounting to USD 60 000. Reporting for this study is expected in mid-2014. Funding is required for monitoring and supervision. Other needs identified are training for health workers and a research coordinator, as well as support for a reference laboratory.

Needs common among these three countries (Vanuatu, Solomon Islands, Papua New Guinea) include training and competency assessment for microscopists. There is also a common need to have Level 1 microscopists in the countries and better microscopists placed in the actual TES sentinel sites.

Each of the countries also raised the issue of funding for a research coordinator and there were discussions on the capacity building required on the operational level for the field teams to collect data. This implies that these needs have not always been met.

All countries also mentioned the need for additional support in terms of external monitoring of the studies. It was interesting to see a lot of common needs as well as capacity within this group of countries. Professor Peter Siba committed that PNG-IMR is very willing to support Solomon Islands and Vanuatu in capacity building. This is something that should be noted, taken forward and made a reality.

There is collaboration among the countries with Solomon Islands and Vanuatu already holding annual meetings. It was suggested that PNG also be invited to these meetings. Countries have access to support from reference laboratories like AMI, which has been conducting testing of samples. It was recommended that an arrangement be formalized regarding the testing services of AMI and it was agreed that this would be discussed during the meeting.

Asked what he saw as IMR’s role in the network, as a WHO collaborating centre, Professor Siba replied that they were interested in further malaria training and research but with the decline in cases they lack samples and patients to train on. He affirmed IMR’s openness to providing assistance to all countries in the Western Pacific and even South-East Asia regions should the WHO request this.

2.4.2 Group 2: Philippines and Malaysia

Philippines

TES will be conducted this year in Palawan province, testing artemether-lumefantrine for *P. falciparum* and chloroquine for *P. vivax*. In 2014, the province of Tawi-Tawi will be added to the sites, with artemether-lumefantrine still to be tested for *P. falciparum*, and chloroquine and primaquine for *P. vivax*. The estimated US$ 212500 budget for each of the two years will come from the GFATM and the Philippines Department of Health, National Malaria Program. Refresher microscopy training will be conducted, with monitoring and supervision by the Research Institute for Tropical Medicine. Gaps and needs identified were sentinel site selection, presence of a dedicated TES team, as well as community advocacy from the local government, patient recruitment and follow-up.
Malaysia

Malaysia has conducted a number of TES already but, the studies did not comply with the WHO-recommended protocol. Another round of TES was suggested because the country is now moving towards changing the national malaria drug policy. In June 2013, Malaysia is to adopt ACT for *P. falciparum* but will continue using CQ plus PQ for *P. vivax*. These drugs will be the ones tested in the TES for all species, in two proposed sites – Sabah and Sarawak.

Potential problems include the enrolment of patients and the recruitment of staff to be dedicated to the TES. The selected sites have limited road access and there are no laboratory facilities. Alternative sites that are more accessible to patients will be chosen to ensure follow-up. The rapid turnover of staff in the health sector will be targeted.

In terms of resources and inputs, Malaysia’s TES is fortunate to have been able to obtain national government support although external support has played a major part as well. Retraining will be conducted and national QA for malaria microscopy will be established.

Malaysia has PCR facilities but there is no national consensus on whether PCR-adjusted microscopy results will be used as confirmatory diagnostic method. Dr Bustos clarified that specifically for the TES, PCR-corrected ACPR is only for the cases that fail. This is when there is a need to get a confirmation if the failure is due to a recrudescence or a reinfection for falcifarum. The Day 0 sample and the day of failure sample for the patient are subjected to PCR. PCR confirmation is required for all slides that are diagnosed positive during follow-up.

This will also be important for Malaysia since *P. knowlesi* is prevalent in certain parts of the country. Using PCR will confirm *Pk* and it will be the first study to look at the efficacy of AL on *Pk*.

On the issue of G6PD screening, Dr Lasse Vestergaard explained that the question of primaquine is important and that the WHO standard TES protocol also covers vivax TES. It can be decided to postpone primaquine treatment until after the 28th day of follow-up for the first-line treatment, at which point the standard low-dose (0.25 mg/kg) primaquine is given for 14 days. But primaquine treatment may also be given from Day 1, which is logistically easier, since primaquine does not affect asexual parasites. Most of the countries give primaquine within their TES schedule but with standard precautions. Likewise, if a country uses primaquine in single dose for *Pf*, they can still give the primaquine along with the first-line treatment because it will not interfere with the efficacy of this. They will not be required to test for G6PD for that single dose of primaquine.

2.4.3 Group 3: Timor-Leste and Indonesia

Timor-Leste

Antimalarials used for TES in East Timor include artemether-lumefantrine for *P. falciparum*, and chloroquine for *P. vivax*. There are a total of four sentinel sites, with a total budget of US$ 126 940 for TES for the years 2013 and 2014. The budget includes allocation for human resource, transport, supplies, technical assistance, and other components such as a quality assurance system, supervision, capacity-building and laboratory support. They have identified the need for technical assistance in the conduct, analysis and writing of reports for the PCR of *Pv* and *Pf*.

Indonesia

There are a total of six sentinel sites. The total budget requirement is US$ 223 545 which covers expenses for human resource, equipment and supplies, contingency fees for clinical trials, patient costs, technical assistance, supervision and quality assurance system. Drug to be monitored is DHP for *Pf* and *Pv*.
A common concern between the two countries is the need to set up a sentinel site at the border (East Timor and West Timor). Both countries are open to cross-border collaboration. It was suggested that coordination be established through WHO or with the neighboring districts as to ensure a more efficient implementation of malaria control activities. Representatives from both Timor-Leste and Indonesia agreed to explore all avenues for collaboration and to further discuss the specific steps.

2.4.4 Summary

In general, all countries are eager to conduct the TES. The gaps identified are primarily on microscopy capacity building (competency). The Pacific Islands countries are also asking for training on research coordination and an external monitor from WHO.

The drug being tested in TES in most countries is AL for *P. falciparum*, except for Indonesia. For *P. vivax*, some countries still use chloroquine, while Indonesia, Papua New Guinea, Solomon Islands and Vanuatu now use ACTs.

All the countries conduct studies for both *P. falc* and *P. viva*, except Malaysia. *P. kii* is considered a big challenge for Malaysia. PCR confirmation takes time but this should be considered in the TES for *P. kii*. It was also suggested that a regional reference laboratory for PCR be identified (or established) to address country needs.

2.5 Technical Session 4: Role and *modus operandi* of the Pacific Malaria Drug Resistance Monitoring Network

2.5.1 Partner collaboration and role of research institutions in national drug efficacy monitoring

Dr Manuel Hetzel, Senior Scientific Collaborator of the Swiss Tropical and Public Health Institute and with several years of work experience with Papua New Guinea through IMR, started the discussion by presenting the relationship between operational research and routine drug efficacy monitoring. As per the Global Plan for Artemisinin Resistance Containment, research required on artemisinin resistance includes: (1) laboratory research; 2) research and development; (3) applied and field research; (4) operational research and (5) mathematical modelling. The focus of the presentation was the conduct of effective and sustainable country-level drug efficacy monitoring which comprises many different components.

Dr Hetzel emphasized the importance of a common agenda that should be set by the Ministry of Health and the research institution to avoid clash of interests. Another issue he cited was the need to have a way for research institutions to share data for policy-makers to use while awaiting formal publication. He said these issues should be discussed by the partners at the outset.

The capacity requirements for implement country-level drug efficacy monitoring include finance, staff, medical, laboratory, scientific, data management and information technology, in addition to administrative and contextual (institutional support, study population, basic infrastructure) requirements.

Rarely can only one single organization cover all these requirements or areas of expertise. Rather, partners with different capacities can complement each other, and equal and fair partnership increases ownership and local capacity. Dr Hetzel presented various potential national and international partners.

He also compared the potential role of implementing agencies and research institutions in drug efficacy monitoring. He cited guide questions to help in making the strategic decision as to whether capacities within the agency/institution can be developed, or whether external collaborators should be sought. Dr Hetzel cited as an example the drug resistance monitoring collaboration taking place in
Papua New Guinea and stressed the importance of local capacity building. He concluded by presenting key principals required for an equitable and effective collaboration. He emphasized that transboundary and intercultural research in partnership is a continuous process of sound knowledge generation, building mutual trust, mutual learning and shared ownership.

In the discussion that followed, Dr Hetzel emphasized the importance of addressing the gaps identified during the country presentations and ensuring support for the countries in what they are already doing and in filling those gaps. He also raised the need for WHO (and other stakeholders) to acknowledge the source of information whenever data is used for further dissemination. He commented that it was not only fair for research institutes but also for the NCMP or the Ministry of Health to receive proper acknowledgement for the data they have shared.

Some countries shared their experiences in conducting research. The Philippines cited the need for an institutional policy regarding the storage of specimens and to include in the consent form the possibility that the patient’s blood may be used for other studies. In Malaysia, a regular forum is held for relevant stakeholders to discuss the research agenda of the health sector. This minimizes overlapping of similar research projects and maximizes the limited resources. Timor-Leste has a similar venue for discussing priority research needs with the NMCP and potential partners. This provides an opportunity to develop consensus on important issues to guide collaboration. Indonesia highlighted its collaboration with the Asia Pacific Malaria Elimination Network (APMEN) and researchers from universities and other institutes.

Dr Hertzel synthesized the discussion by emphasizing the importance of collaboration in research and the need for constant dialogue and establishment of clear agreements on the various aspects of planning and conduct of the study. He felt that research should have a general interest of supporting the needs of the ministries of health.

2.5.2 Capacity building and funding

Dr Dorina Bustos of WHO Thailand presented on capacity building for drug efficacy monitoring and funding. TES training workshops, data management and refresher microscopy must be completed prior to the TES. Other activities to be carried out are field site monitoring with principal investigators to ensure quality implementation, data validation with a WHO expert, external slide validation with a WHO Level 1 Microscopist, report writing and publication. The national programme TES staff must also be trained on quality control procedures in general, and countries must have a core group of “qualified” microscopists (WHO-certified) assigned to TES who periodically undergo proficiency testing and retraining to ensure quality in malaria diagnosis and counting.

Other capacity-building activities include those for molecular laboratory and reference laboratories. Crucial also are cross-country monitoring between principal investigators to observe and learn best practices, regional and national coordination meetings and venues for information-sharing. For specific situation protocols, training is focused on TES in areas with very low transmission, and TES in pre-elimination areas.

Dr Bustos concluded her presentation by highlighting a valuable lesson based on the Greater Mekong Subregion experience – that assured long-term support and the presence of multiple partners with different areas of expertise allows flexibility to incorporate institutional capacity building, which facilitates strengthening of country TES teams over the years.

2.5.3 Workplan, communication and coordination of the Pacific network

Dr Lasse Vestergaard, Medical Officer, Malaria, other Vectorborne and Parasitic Diseases, WHO Philippines enumerated the different activities outlined for the Pacific Malaria Drug Resistance
Monitoring Network for years 2013 and 2014. These include (1) provision of day-to-day coordination and technical support for TES implementation; (2) provision of TES on-site supervision and monitoring visits; (3) organization of regional training workshops on relevant topics; (4) facilitation of laboratory support if not available (e.g. from identified regional laboratories); (5) facilitation of standardization of laboratory SOPs and QA systems; (6) establishment of a regional database of TES results; (7) assistance in priority operational research as identified by countries; (8) organization of one annual meeting for countries to share results and address technical and operational issues; and (9) facilitation of communication and collaboration. Resources for the network within the same year include funding for the implementation of 1–2 TES sites per country, one annual network meeting, network training workshops and collaborative meetings and one full-time network staff based in WHO-WPRO for coordination of activities and day-to-day technical support.

In the discussion that followed, clarifications were made about the composition and terms of reference of the network. Dr Christophel pointed out that it is a country-led network so it is up to the countries to decide. The terms of reference defined two years ago are subject to discussion and revision as needed. It was agreed that the country members would give the names of the focal points for their respective countries once they had confirmed with these persons.

2.6 Technical Session 5: Supportive action

2.6.1 Health research involving human subjects: ethical considerations and procedures to follow

Dr Manju Rani, Senior Technical Officer, Health Research Policy of the WHO Regional Office for Western Pacific began the discussion by pointing out that a research study is ethical when guiding principles intended to protect the rights and interests of human subjects are followed. These are the principles of beneficence, justice and respect for persons. She further elaborated on the manner in which each of these three principles can be applied to TES.

Key ethical issues in TES were discussed next which included: (1) the high burden on recruited patients (more than during routine care); (2) the heavy burden on health facilities; (3) the dependent relationship between the researcher and participant and resulting potential coercion; (4) testing the efficacy of second-line drugs or newly registered ACTs; (5) whether the exclusion criteria is appropriately followed; (6) enrolment of young infants and children; (7) inability to recruit sufficient sample size; and (8) the number of TES studies considered optimal.

The importance of the role of the research team and independent review committee was also highlighted in terms of the responsibility for ensuring the ethical conduct of a study. Several reasons were cited for the need to have an independent review by a committee including historical reasons (e.g. past high-profile reports on neglect/misuse of rights and interests of human research participants by even well-trained and well-respected researchers), and several publications documenting that ethical problems were mainstream, not merely on the fringes. The current mechanisms for an independent review were also discussed.

The last part of the discussion pertained to national ethics committees and the WPRO Ethics Review Committee, particularly SOPs and structure. She informed the body that such information can be accessed at the WPRO external website. Research studies for review by the WPRO-ERC can be submitted online. She also cited the different types of reviews depending upon the type of study proposal, as well as the benefits of having such a review.

Dr Rani concluded that the trust and confidence of study participants are essential to ensure their participation and the success of the TES. To continue the studies, their rights and interests must be respected, benefits maximized and harms minimized. Ethical conduct is not ensured by a review committee. It is the research team that is primarily responsible for ensuring the ethical conduct of research.
In the discussion that followed, Dr Jean Olive Guintrant, Medical Officer for Malaria, other Vectorborne and Parasitic Diseases, WHO Vanuatu Office, suggested that the network take on the task of strengthening the capacity of countries in setting up ethical review committees. Dr Rani agreed with this and affirmed that she had been actively working with countries to improve their capacity. She said that aside from training ethics committee members, they are also assisting countries to bring an optimal balance to the research process, and simplifying procedures using a multi-dimensional approach. She cited the example of Lao Democratic People’s Republic where they introduced the online submission of proposals which reduced the time to conduct the review and expedited the results. She pointed out that for very small Pacific Island countries which may not have the critical mass of people to actually carry out a review, the country could outsource the review to an external ethics committee.

She assured the Member States that if they feel they have the internal capacity, then WHO will support them to constitute it. She emphasized that the problem in developing countries is that the researchers themselves are not trained or are trained in the wrong way. They think that ethics is just getting approval from an ethics review committee. They hold this mistaken perception which WHO has the responsibility to correct.

2.6.2 Implementation of quality assurance for malaria microscopy in TES

Dr Dorina Bustos presented the results of the external assessment of microscopy from a TES in Country X (unspecified country). She began by stating the purpose of the blood film validation was not fault-finding, but rather to further enhance the skills of the microscopists and help improve the support system for delivering microscopy services. She also showed pictures of macroscopically good smears, poor smears, poor thick films and blood smears from actual sites. General findings were that there were missing/misplaced/broken slides, poor smear preparation and staining and unsatisfactory condition of Giemsa stain, microscopes and other supplies.

In the discussion that followed, the need for capacity building for malaria microscopy to meet the standards and requirements for research was emphasized. Dr Hetzel pointed out that the health workers or laboratory technicians involved in routine clinical work in health facilities or hospitals often do not have the level of proficiency required for a research setting.

2.6.3 Operational research to enhance drug efficacy monitoring, prevent drug resistance and optimize treatment of malaria

Dr Lasse Vestergaard initiated the discussion by reviewing the four action pillars of the GPARC, as previously presented by Dr Christophel. He then went on to specify the objectives of the EARAP plan which are to: (1) fast-track key operational research projects across countries; (2) refine existing tools to improve operations; (3) enhance timely sharing of information and use of evidence to inform national guidelines; and (4) stimulate collaborative research and maximize the use of resources and skills.

Dr Vestergaard also presented priority areas for operational research, including (1) mass drug administration for elimination of artemisinin-resistant parasites; (2) use of gametocytocidal drugs (primaquine); (3) development and use of more sensitive diagnostic tools; (4) molecular markers for artemisinin-resistance; and (5) multiple first-line antimalarial therapies. Activities for the refinement of tools for drug efficacy monitoring include ACD, FSAT and MSAT, improvement of reporting methods for more timely operations, triggering response to plans and establishment of vector control methods.
2.6.4 Summary

The group was reminded of the principles of ethics in research, particularly for the conduct of TES and that everyone is responsible for the ethical conduct of research. The presentation on the microscopy in some countries and what is needed to improve quality is useful for member countries in their efforts to strengthen malaria microscopy for TES. Research agendas are not only relevant to the containment of artemisinin resistance but also to the ongoing malaria elimination efforts in several countries.

3. CONCLUSION AND RECOMMENDATIONS

In the plenary discussion, Dr Christophel presented the draft conclusions and recommendations of the meeting.

The following are the conclusions based on the two-day network meeting:

1) All seven member countries since the last meeting have conducted or are about to conduct TES and have plans for the next two years;

2) The network founded two years ago contributed to the harmonization of the TES across the countries of the network;

3) The network, due to the recent availability of funding, is now ready to support country-level TES and conduct regional activities and effectively coordinate drug resistance monitoring in the region;

4) Each country presented TES results and experiences and identified gaps and needs;

5) The exchange of information led to the revision and harmonization of country plans 2013–2015;

6) The need for capacity building in all levels of TES implementation was highlighted;

7) The TES activities for the next two years are largely funded by the Global Fund and AusAID, but sustainability is an issue;

8) A number of common challenges were identified such as difficulty reaching adequate sample size in view of the decline in malaria patient numbers, definition of sentinel sites, duration of recruitment, quality assurance for malaria microscopy, laboratory support for molecular analysis, migration and human resources;

9) The current TES involves a variety of partners, but the network would profit from strengthening existing partnerships and establishing new ones;

10) Given the emergence of the artemisinin resistance in the GMS, intensification of drug resistance monitoring throughout the region is essential.

Recommendations of the meeting:

1) Ensure that the TES country plans are fully implemented as planned and to a high standard, following WHO standard protocol including analysis of Day 3 positivity data (as an indicator for artemisinin resistance) as part of the TES. Priority should be given to first-line drugs;
2) The network with the funding now available should support countries to address identified gaps and needs in TES implementation;

3) The network should support regional- and country-level capacity building (including cross-country visits) in areas relevant to the implementation of the TES;

4) The network should contribute to strengthening existing partnerships and facilitating the establishment of new ones, where needed. Partnerships should be built on common interest and mutual benefit and the agenda should be set together;

5) The network should facilitate the exchange of data and information at regional and country level;

6) The network should support independent monitoring of TES, quality assurance of microscopy and data validation as key regional activities;

7) The network should encourage and facilitate operational research that contributes to improved drug efficacy monitoring and prevention of artemisinin resistance;

8) The network and countries should be actively engaged in securing long-term funding;

9) The next network meeting should take place in one year in Malaysia.
# TIMETABLE

## 2nd PACIFIC MALARIA DRUG RESISTANCE MONITORING NETWORK MEETING

**06-07 May 2013 – Manila, Philippines**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Time</th>
<th>Session/Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>Registration</td>
<td></td>
</tr>
</tbody>
</table>
| 8:30  | Opening Ceremony | Opening remarks by the Regional Director WHO WPRO
Self-introduction of participants
Nomination of Chair, Vice Chairs and Rapporteur
Group photograph |
| 9:15  | Tea/Coffee Break | |
| 9:45  | Session 1: Update on antimalarial drug efficacy monitoring and resistance *(10 minute presentations followed by 5 minutes discussion)* | Global update on tracking and mapping of antimalarial drug efficacy and drug resistance – Ms Amy Barrette, WHO GMP/HQ
Update on antimalarial drug resistance in the Western Pacific Region and progress with the Pacific Monitoring Network – Dr Eva Christophel, WHO WPRO
Update on antimalarial drug resistance in the South East Asian Region – Dr Anand Joshi, WHO SEARO
The role of country networks in antimalarial drug efficacy monitoring and prevention of drug resistance: Update and lessons from the Mekong Malaria Network – Dorina Bustos, WHO Thailand
Overview of Emergency Response to Artemisinin Resistance in the GMS – Dr Eva Christophel, WHO WPRO |
| 10:00 | Discussion | Wrap-up & recommendations - Qin Cheng, Australia Army Institute |
| 11.30 | Session 2: Country updates: | Malaria situation, treatment policy, drug resistance situation and monitoring, technical issues *(10 minute presentations followed by 5 minutes discussion)*
- Papa New Guinea, Solomon Islands, Vanuatu |
| 12:15 | Lunch | |
### Session 2: continued

13:15 - Philippines, Malaysia  
13:45 - East Timor, Indonesia  
14:15 Discussion  
   Wrap-up & recommendations - Lasse Vestergaard, WHO Philippines

### Session 3: Update on technical issues to strengthen drug resistance monitoring

14:30 Update on methods for antimalarial drug resistance monitoring and use of the WHO standard protocol, practical issues, sentinel site selection, frequency of studies, data analysis, reporting of results – Dorin Bustos, WHO Thailand  
14:50 Update on laboratory methods to monitor antimalarial drug resistance – Qin Chen, Australia Army Institute  
15:10 Discussion  
   Wrap-up & recommendations - Dr Emiliana Tjitra, MOH Indonesia  
15:30 *Afternoon Tea/Coffee*

### 16:00 Group work:


Introduction to group work  
**Tasks:**  
1. Draft 2-year national plans (where, what, who)  
2. Identify resources available, role of partners  
3. Identify support needed (technical, training, funds, other) from the Pacific Network

**Groups:**  
1. Papa New Guinea, Solomon Islands, Vanuatu + partners  
   – *Facilitators: Dr Walther Kazadi and Dr Manuel Hetzel*  
2. Philippines, Malaysia + partners  
   – *Facilitators: Dr Emiliana Tjitra and Dr Lasse Vestergaard*  
3. East Timor, Indonesia + partners  
   – *Facilitators: Dr Dorina Bustos and Dr Anand Joshi*

### 17:30 Close for the Day  
18:00 Refreshments hosted by WHO
## DAY 2

### 8:30
**Summary of Day 1** by Zaixing Zhang, WHO Solomon Islands, and Jean Olivier Guintran, WHO Vanuatu

### 8:45
**Presentation of Group work:**
- 20 minute presentations followed by 10 minutes discussion per group (3 groups)
  - Country work plans for routine efficacy monitoring
  - Resources available, role of partners
  - Role of and support needed from the Pacific network

### 10:15
Discussion
Wrap-up & recommendations - Dr Emiliana Tjitra, MOH Indonesia

### 10:30
**Tea/Coffee Break**

### 11:00
**Session 4: Role and Modus Operandi of the Pacific Malaria Drug Resistance Monitoring Network**
- Partner collaboration and role of research institutions in national drug efficacy monitoring – Manuel Hetzel, Swiss Tropical Institute, Switzerland
- Capacity building, funding – Dorina Bustos, WHO Thailand
- Work plan, communication and coordination of the Pacific Network – Lasse Vestergaard, WHO Philippines

### 11:45
Discussion
Wrap-up & recommendations – Amy Barrette, WHO GMP/HQ

### 12:00
**Lunch**

### 13:00
**Session 5: Supportive action**
- Health research involving human subjects: ethical considerations and procedures to follow - Manju Rani, WHO WPRO

### 13:20
Implementation of quality assurance for malaria microscopy in TES - Dorina Bustos, WHO Thailand

### 13:40
Operational research to enhance drug efficacy monitoring, prevent drug resistance and optimize treatment of malaria – Lasse Vestergaard, WHO Philippines

### 14:00
Discussion
Wrap-up & recommendations – Qin Cheng, Australia Army Institute

### 14:30
**Afternoon Tea/Coffee**

### 15:00
**Meeting conclusions and recommendations, next steps** - Eva Christophel, WHO WPRO

### 16:00
**Closing**
LIST OF PARTICIPANTS,
TEMPORARY ADVISERS, REPRESENTATIVES/OBSERVERS
AND SECRETARIAT

1. PARTICIPANTS

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

Mr Joko Waluyo
Perumahan YKP Pandugo 2
Jl Pandugo Timor SV/F-40
Surabaya 60297
Tel No : +62 855336868600
E-mail : jokobluer@yahoo.co.id

MALAYSIA
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
Tel No : +603 8883 4268/+6012 359 0017
E-mail : Drmhafizi@moh.gov.my
Dr Raden Shamilah binti Radin Hisham  
Medical Research Specialist Officer  
Institute for Medical Research  
Jalan Pahang  
50588 Kuala Lumpur  
Tel No : +603 2616 2682/+6016 283 9795  
E-mail : shamilah@iMrgov.my

PAPUA NEW GUINEA  
Mr Leo Makita  
Programme Officer, Malaria and other Vector Borne Diseases  
Department of Health  
P.O. Box 807  
Waigani  
Tel No : +675 3013819  
E-mail : leo.makita@gmail.com ; leo_makita@health.gov.pg

Professor Peter Siba  
Director  
Papua New Guinea Institute of Medical Research  
P.O. Box 60  
Goroka  
Tel No : +675 5322800  
E-mail : peter.siba@pngiMrorg.pg

PHILIPPINES  
Dr Mario Baquilod  
Medical Officer V/In Charge of  
Infectious Diseases Office  
National Center for Disease Prevention & Control  
Department of Health  
San Lazaro Compound  
Manila  
Tel No : +632 9973399  
E-mail : marbaquilod@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  
Tel No : +632 807 2628 to 32, loc 227/804  
E-mail : fe.espino2012@gmail.com

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

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

TIMOR-LESTE  
Mr Raul Sarmento  
National Malaria Programme Manager  
National Malaria Control Programme  
CDC Department, NOH  
Lahane Osidental  
Dili  
Tel No : +670 732 6631  
E-mail : raul.sarmento@mohedc.gov
Ms Maria Do Rosario de Fatima Mota  
National Malaria Officer  
Marconi-Fatuhada  
(beside Cooperative Office)  
Dili  
Tel No  :  +670 773 24403  
E-mail  :  mariamota_79@yahoo.com

VANUATU

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

Mr Esau Naket  
Malaria Nurse Practitioner  
National Malaria Control Programme  
Ministry of Health  
PMB 909  
Port Vila  
Tel No  :  +678 7752427  
E-mail  :  enaket@vanuatu.gov.vu

2. TEMPORARY ADVISERS

ARMY MALARIA INSTITUTE

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

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
Tel No : +62 21 3102849
E-mail : emilt@litbang.depkes.go.id; etjitra@yahoo.com

SWISS TROPICAL AND PUBLIC HEALTH INSTITUTE

Dr Manuel Hetzel
Senior Scientific Collaborator
Swiss Tropical & Public Health Institute
Health Interventions Unit
Socinstrasse 57
P.O. Box CH 4002
Basel
Switzerland
Tel No : +4161 2848168
E-mail : Manuel.hetzel@unibas.ch

3. SECRETARIAT

WHO WPRO

Dr Eva Maria Christophel
Team Leader
Malaria, Other Vectorborne and Parasitic Diseases
The World Health Organization
Regional Office for the Western Pacific
P.O. Box 2932
1000 Manila
Philippines
Tel No : +632 528-9723
E-mail : christophele@wpro.who.int
Dr Bayo Fatunmbi  
Technical Officer (Monitoring & Evaluation)  
Malaria, Other Vectorborne and Parasitic Diseases  
The World Health Organization  
Regional Office for the Western Pacific  
P.O. Box 2932  
1000 Manila  
Philippines  
Tel No : +632 528 9725  
E-mail : fatunmbib@wpro.who.int

WHO INDONESIA  
Dr Anand Joshi  
Technical Officer, Malaria  
WHO Indonesia  
Bina Mulia I, Floor 9, Jl HR Rasuna Said Kav  
10-11 Kuningan  
Jakarta  
Tel No : +62215204349  
E-mail : joshia@searo.who.int

WHO PAPUA NEW GUINEA  
Dr Walter Kazadi Mulombo  
Scientist  
Malaria, Other Vectorborne and Parasitic Diseases  
World Health Organization  
4th Floor, AOPI Center  
Waigani Drive  
Port Moresby  
Tel No : +675 325 7827  
E-mail : kazadimulombow@wpro.who.int
WHO PHILIPPINES

Dr Lasse Vestergaard
Medical Officer
Malaria, Other Vectorborne and Parasitic Diseases
World Health Organization
National Tuberculosis Centre Building
Second Floor, Bldg 9
Department of Health'
San Lazaro Hospital Compound
Sta Cruz, Manila
Tel No  :  +632 528 9061
E-mail  :  vestergaardl@wpro.who.int

Ms Arlene Leah Rosal Santiago
SSA, Malaria, Other Vectorborne and Parasitic Diseases
World Health Organization
National Tuberculosis Centre Building
Second Floor, Bldg 9
Department of Health'
San Lazaro Hospital Compound
Sta Cruz, Manila
Tel No  :
E-mail  :  leahrlyn08@yahoo.com

Ms Jeunessa Sto Niño
SSA, Malaria, Other Vectorborne and Parasitic Diseases
World Health Organization
National Tuberculosis Centre Building
Second Floor, Bldg 9
Department of Health'
San Lazaro Hospital Compound
Sta Cruz, Manila
Tel No  :
E-mail  :  jeunessa.stonino@gmail.com
WHO TIMOR-LESTE
Dr Manel Yapabandara
Technical Officer, Malaria
WHO Timor-Leste
P.O. Box 451
Dili
Tel No : +670 33 10968
E-mail : yapabandaraa@searo.who.int

WHO THAILAND
Dr Maria Dorina Bustos
Technical Officer, Malaria
WHO-Mekong Malaria Programme
Office of the WHO Representative to Thailand
Permanent Secretary Building 3, 4th Floor
Ministry of Public Health
Tiwanon Rd, Nonthaburi 11000
Tel No : +66 2 5918198/66 2 5901524
Mob: +660 853349909
E-mail : bustosm@searo.who.int
dorinabustos@yahoo.com

WHO SOLOMON ISLANDS
Dr Zhang Zaixing
Medical Officer
Malaria, Other Vectorborne and Parasitic Diseases
World Health Organization
Ministry of Health Building
Honiara
Tel No : +677 22053
E-mail : zhangz@wpro.who.int
**WHOA VANUATU**

Dr Ros Seyha  
Scientist  
Malaria, Other Vectorborne and Parasitic Diseases  
World Health Organization  
MOH Iatika Complex  
P.O Box 177  
Port Vila  
Tel No : +678 27683  
E-mail : ross@wpro.who.int

Dr Jean-Olivier Guintran  
Medical Officer  
Malaria, Other Vectorborne and Parasitic Diseases  
World Health Organization  
MOH Iatika Complex  
P.O Box 177  
Port Vila  
Tel No : +678 27683  
E-mail : guintranjwpro.who.int

**WHO/HQ**

Ms Amy Barrette  
Technical Officer  
Drug Resistance and Containment  
HQ/GMP Malaria Programme  
World Health Organization  
Avenue Appia 20  
1211 Geneva 27  
Switzerland  
Tel No : +4122 7911648  
E-mail : barrettea@who.int
4. OBSERVERS

ASIA PACIFIC MALARIA ELIMINATION NETWORK (APMEN)

Ms Arna Chancellor
Programme Manager
APMEN Joint Secretariat
University of Queensland Office
Room 305 Edith Cavell Building
School of Population Health
Herson Road, Herson
Queensland 4006
Australia
Tel No : +61 7 3365 5446
E-mail : a.chancellor@uq.edu.au

SECRETARIAT OF THE PACIFIC COMMUNITY

Ms Lilian Sauni
Solomon Islands Grant Coordinator
SPC Headquarters, BP D5
98848 Noumea Cedex
New Caledonia
Tel No : +687 262000
E-mail : LilianS@spc.int
### COUNTRY TES PLANS

#### 1. Philippines

<table>
<thead>
<tr>
<th>Name of site</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
<th>Name of site</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
<th>Refresher Microscopy training</th>
<th>Monitoring and supervision</th>
<th>Other needs/gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palawan - about to start</td>
<td>Pf - AL, Pv - Cq</td>
<td>USD87,500 (GF - operations, travel, etc.)</td>
<td>Palawan: Puerto Princesa.</td>
<td>Pf - AL, Pv - Cq; Pq</td>
<td>USD87,500</td>
<td>Yes</td>
<td></td>
<td>By RITM</td>
</tr>
<tr>
<td>Palawan - about to start</td>
<td>Pf - AL, Pv - Cq</td>
<td>USD125,000 (GoP - commodities; full time personnel)</td>
<td>Palawan: Bataraza, Brooke’s Point and Rio Tuba Nickel Foundation.</td>
<td>Pv (Pq 30 mg)</td>
<td></td>
<td>Yes</td>
<td></td>
<td>Sentinel site and dedicated sentinel TES team; RTN Foundation - community advocacy, patient recruitment, follow-up.</td>
</tr>
<tr>
<td>Tawi-Tawi</td>
<td>Pf - AL</td>
<td>USD125,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feasibility study for potential site</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>USD 212,500</td>
<td></td>
<td><strong>Total</strong></td>
<td>USD 212,500</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 2. Papua New Guinea, Solomon Islands, Vanuatu

<table>
<thead>
<tr>
<th>Country</th>
<th>2013</th>
<th>2014</th>
<th>Proposed</th>
<th>Refresher Microscopy training</th>
<th>Monitoring and supervision</th>
<th>Other needs/gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Papua New Guinea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Funds for microscopy capacity building (formal annual 2-3 week refresher training as previously recommended by AMI) &amp; continuation of annual competency assessment by AMI.</td>
</tr>
<tr>
<td>Parasite species</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Funds for dissemination of results</td>
</tr>
<tr>
<td>Drugs to test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Funds for dissemination of results</td>
</tr>
<tr>
<td>Proposed budget</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Funds for dissemination of results</td>
</tr>
<tr>
<td><strong>Papua New Guinea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasite species</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs to test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proposed budget</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- AL: GFATM until Oct 2014
- DHA-PPQ: GFATM until Oct 2014
<table>
<thead>
<tr>
<th>Country</th>
<th>2013</th>
<th>2014</th>
<th>Other needs/gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name of site</td>
<td>Parasite species</td>
<td>Drugs to test</td>
</tr>
<tr>
<td>Solomon Islands</td>
<td>Tere &amp; Auki/ Malaita</td>
<td>Pf &amp; Pv</td>
<td>AL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solomon Islands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanuatu</td>
<td>Santo Island, Sanma Province</td>
<td>Pf &amp; Pv</td>
<td>AL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 3. Timor-Leste

<table>
<thead>
<tr>
<th>Name of site</th>
<th>Parasite species</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
<th>Name of site</th>
<th>Parasite species</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
<th>Refresher microscopy training</th>
<th>Monitoring and supervision</th>
<th>Other needs/ gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. South and East</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lospalos CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Lospalos CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Yes</td>
<td></td>
<td>PCR for Pf and Pv</td>
</tr>
<tr>
<td>Viqueque Vila CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td>Viqueque vila CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td>Yes</td>
<td>TA for analysis and report writing</td>
</tr>
<tr>
<td>Uatulari CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td>Uatulari CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uatucarbau CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td>Uatucarbau CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Dili district (Northern part)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comoro CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Comoro CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Yes</td>
<td></td>
<td>PCR for Pf and Pv</td>
</tr>
<tr>
<td>Centro CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td>Centro CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td>Yes</td>
<td>TA for analysis and report writing</td>
</tr>
<tr>
<td>Vemasse CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td>Vemasse CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laga CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td>Laga CHC</td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name of site</td>
<td>Parasite species</td>
<td>Drugs to test</td>
<td>Proposed budget</td>
<td>Name of site</td>
<td>Parasite species</td>
<td>Drugs to test</td>
<td>Proposed budget</td>
<td>Refresher microscopy training</td>
<td>Monitoring and supervision</td>
<td>Other needs/ gaps</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------------------</td>
<td>---------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>3. Atauro Island</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atauro CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Atauro CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Yes</td>
<td></td>
<td>PCR for Pf and Pv, TA for analysis and report writing</td>
</tr>
<tr>
<td></td>
<td>Pv</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. East and West Timor border</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balibo CHC</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Suai Vila</td>
<td>Pf</td>
<td>AL</td>
<td>USD 24,700</td>
<td>Yes</td>
<td></td>
<td>PCR for Pf and Pv, TA for analysis and report writing</td>
</tr>
<tr>
<td></td>
<td>Pv</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td>Pf</td>
<td>Chloroquine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suai Vila</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>USD 126,940</strong></td>
<td><strong>Total</strong></td>
<td><strong>USD 126,940</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 4. Indonesia

<table>
<thead>
<tr>
<th>Name of site</th>
<th>Parasite species</th>
<th>Drugs to test</th>
<th>Proposed budget</th>
<th>Refresher Microscopy training</th>
<th>Monitoring and supervision</th>
<th>Other needs/ gaps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mimka - Papua island</td>
<td>P. falciparum</td>
<td>DHA-PIP</td>
<td>USD 223,545</td>
<td>Internal (national)</td>
<td>External (consultant)</td>
<td></td>
</tr>
<tr>
<td>Tomohon- North Sulawesi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sikka –Flores- East Nusa</td>
<td>P. vivax</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenggara - East Kalimantan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samalinda- East Kalimantan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangka Belitung Island - North Halmahera</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Maluku</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.2.3. Measurement of body temperature

Axillary temperature will be performed at baseline (day 0 pre-dose) as well as on days 1, 2, 3, 7, 14, 21, 28, 35, 42.

1) Temperature will be measured using a thermometer with a precision of 0.1°C. Temperature will additionally be measured as clinically indicated.

2) If the result is <36.0°C, the measurement will be repeated.

Quality of temperature-taking technique and thermometers should be regularly tested in a water-bath of known temperature prior to study commencement and at regular intervals during study.

6.2.4. Microscopic blood examination

Thick and thin blood films for parasite count should be obtained and examined at screening on day 0 to confirm inclusion/exclusion criteria. Thick blood films will be also examined on days 2, 3, 7, 14, 21, 28, 35, and 42 or on any other day if the patient spontaneously returns and parasitological reassessment is required. Specimens will be labelled anonymously (screening number or study number, day of follow-up, date).

Fresh Giemsa stain dilution will be prepared at least once each day and possibly more often, depending on the number of slides being processed. Giemsa-stained thick and thin blood film will be examined at a magnification of 1000x to identify parasite species and determine parasite density.

Three blood slides per patient will be obtained: two thick blood smears and one thin blood smear. One slide will then be rapidly stained (10% Giemsa for 10–15 minutes) for initial screening of patients, while the others are retained. Should the patient subsequently be enrolled, the second slide will be stained more carefully (e.g. 2.5–3% Giemsa for 45–60 minutes). This slower staining method will also be used for all slides obtained during patient follow-up visits. The study number of the patient, the date and the day of follow-up will be recorded either on the frosted edge of the slide or on the glass with a permanent glass pen.
The thick blood smear for initial screening will be examined by counting the asexual parasites and white blood cells in a limited number of microscopic fields. Adequate parasitaemia for enrolment requires at least 1 parasite for every 6 white blood cells, corresponding to approximately 1000 asexual parasites/µl, for low to moderate transmission areas.

The second blood smear will be used to calculate the parasite density of enrolled patients. Blood smears taken during patient follow-up will be examined in the same manner.

(1) Parasite density will be calculated by counting the number of asexual parasites against a set number of white blood cells (WBCs) — typically 200 or 300 — in the thick blood film, using a hand tally counter.

(2) Once a field has been started, it will always be counted to completion; the final WBC count will therefore rarely be exactly 200.

(3) If more than 500 parasites have been counted before 200 WBCs have been reached, the count will be stopped after the reading of the last field has been completed. Parasite density, expressed as the number of asexual parasites per micro litre (µl) of blood, will be calculated by dividing the number of asexual parasites by the number of WBCs counted and then multiplying by an assumed WBC density (typically 6000 WBCs/µl).

(4) Parasite density/µl = \[
\frac{\text{Number of parasites counted} \times 6000}{\text{Number of leukocytes counted}}
\]

The same technique will be employed for establishing parasite counts on each of the subsequent blood film examinations. Parasitaemia will be measured by counting the number of asexual parasites against the number of WBCs in the thick blood film.

(5) When the number of asexual parasites is less than 10 per 200 WBCs in follow-up smears, counting will be done against at least 500 WBCs (i.e. to the completion of the field in which the 500th WBC is counted).

(6) A blood slide will be considered NEGATIVE when the examination of 1000 WBCs does not reveal any asexual parasites. The presence of gametocytes on any enrolment or follow-up slide will be noted, but this information will not contribute to the basic evaluation of the test.

(7) In addition, 100 fields of the second thick film will be examined to exclude mixed infections; in case of any doubt, the thin film will be examined for confirmation. If examination of the thin film is not conclusive, the patient will be excluded from the analysis after complete treatment and follow-up.
(8) Two qualified microscopists will independently read all of the slides and parasite densities will be calculated by averaging the two counts. Blood smears with disconcordant results (differences between the two microscopists in species diagnosis, or differences in parasite density of $\geq 50\%$ or difference in the presence of parasites) will be re-examined by a third, independent microscopist, and parasite density will be calculated by averaging the two most concordant counts. (Third microscopist preferably a WHO “Level 1” expert).

6.2.5. Genotyping of malaria parasites

In order to differentiate a recrudescence (same parasite strain) from a newly acquired infection (different parasite strain), a genotypic analysis based on the extensive genetic diversity displayed by the malaria parasite genes, \textit{msp1}, \textit{msp2} and \textit{glurp} will be performed. Genotypic profiles of the pre- and post parasite strains will be compared.

In order to minimize discomfort to the patient due to repeated finger pricks, two to three drops of blood will be collected on a filter paper Whatman 3MM from each patient during the screening procedure and at each time blood smears are required per protocol (at least day 0, 7, 14, 28, 35, and 42 day or day of recrudescence).

Specimens will be labeled anonymously (study number, day of follow-up, date), kept in individual plastic bags with desiccant pouches and protected from light, humidity and extreme temperature until analyzed. When such room temperature conditions are not possible, for example in extremely humid environments where air-conditioning is not available, storage in a refrigerator or freezer will be considered, but great care will be taken to protect samples from frost and moisture. The PCR technique used will be performed by laboratory ______________. Paired filter papers will be used for parasite DNA extraction and genotyping. Unused filter papers will be kept in safe locations until data are eventually validated or for further research needs.
# FORM FOR SUMMARY OF LABORATORY RESULTS BY PHYSICIAN

Summary of laboratories result by MD

Name: [Name]
Specie: [Specie]
Place of study site: [Place of study site]
Drug: [Drug]
Year: [Year]
Dose/kgw: [Dose/kgw]

<table>
<thead>
<tr>
<th>Code</th>
<th>Patient name</th>
<th>sex</th>
<th>Age</th>
<th>Day</th>
<th>Parasite count T/L</th>
<th>Parasite/μl</th>
<th>Average parasite/μl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MICRO.1</td>
<td>MICRO.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total Divided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td></td>
<td></td>
<td></td>
<td>8000</td>
<td>8000</td>
<td>#DIV/0!</td>
<td>2</td>
</tr>
<tr>
<td>D1</td>
<td></td>
<td></td>
<td></td>
<td>8000</td>
<td>8000</td>
<td>#DIV/0!</td>
<td>2</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td></td>
<td></td>
<td>8000</td>
<td>8000</td>
<td>#DIV/0!</td>
<td>2</td>
</tr>
<tr>
<td>D3</td>
<td></td>
<td></td>
<td></td>
<td>8000</td>
<td>8000</td>
<td>#DIV/0!</td>
<td>2</td>
</tr>
<tr>
<td>D7</td>
<td></td>
<td></td>
<td></td>
<td>8000</td>
<td>8000</td>
<td>#DIV/0!</td>
<td>2</td>
</tr>
</tbody>
</table>
• Global report on antimalarial drug efficacy and drug resistance: 2000-2010. WHO 2010
• Reviewing and planning therapeutic efficacy studies to monitor antimalarial drug resistance in the Greater Mekong Subregion, meeting report, Kunming, 12-13 June 2012 (hard copy)
• Pacific Malaria Drug Resistance Monitoring Network. Meeting Report, Manila, 08-09 August 2011 (hard copy)
• Methods for Surveillance of Antimalarial Drug Efficacy, WHO 2009
• TES template protocol + summary cover sheet
• Methods and techniques for assessing exposure to antimalarial drugs in clinical field studies, WHO 2011 (hard copy)
• Global plan for artemisinin resistance containment (GPARC), WHO 2011
• Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Subregion, 2012
• Regional Action Plan for Malaria Control and Elimination in the Western Pacific (2010-2015), WHO WPRO 2009 (hard copy)
• World Health Assembly resolutions on malaria: 2007, 2011 (hard copies)
• ASEAN commitments:
  • Joint Statement, 11th ASEAN Health Minister Meeting, 5 July 2012, Phuket, Thailand
  • Joint Statement, 5th ASEAN Plus Three Health Ministers Meeting, 6 July 2012, Phuket, Thailand
  • Joint Statement, 4th ASEAN-China Health Ministers Meeting, 6 July 2012, Phuket, Thailand
  • ASEAN Declaration of the 7th East Asia Summit on malaria, Phnom Penh, Cambodia, 20 November 2012 (hard copies)
• Malaria 2012, Sydney:
  • Australian Government, AusAID communiqué, Sydney, 2 November 2012 (hard copy)
  • Malaria 2012 Issues Papers 1-5
LIST OF DOCUMENTS IN USB

1. Timetable
2. Presentations

Session 1: Update on antimalarial drug efficacy monitoring and resistance

- Global update on tracking and mapping of antimalarial drug efficacy and drug resistance (Ms. Amy Barrette, WHO GMP/HQ)
- Update on antimalarial drug resistance in the Western Pacific Region and progress with the Pacific Monitoring Network (Dr Eva Christophel, WHO WPRO)
- Update on antimalarial drug resistance in the South East Asian Region (Dr Anand Joshi, WHO SEARO)
- The role of country networks in antimalarial drug efficacy monitoring and prevention of drug resistance; update and lessons from the Mekong Malaria Network (Dorina Bustos, WHO Thailand)
- Overview of Emergency Response to Artemisinin Resistance in the GMS (Dr Eva Christophel, WHO WPRO)

Session 2: Country Updates: Malaria situation, treatment policy, drug resistance situation and monitoring, technical issues

- Papua New Guinea
- Solomon Islands
- Vanuatu
- Philippines
- Malaysia
- Timor-Leste
- Indonesia

Session 3: Update on technical issues to strengthen drug resistance monitoring

- Update on methods for antimalarial drug resistance monitoring and use of the WHO standard protocol, practical issues, sentinel site selection, frequency of studies, data analysis, reporting of results (Dorin Bustos, WHO Thailand)
- Update on laboratory methods to monitor antimalarial drug resistance (Qin Chen, Australia Army Institute)
- Country TES Plans (Papua New Guinea, Solomon Islands, Vanuatu, Philippines, Timor-Leste, Indonesia)
Session 4: Role and *Modus Operandi* of the Pacific Malaria Drug Resistance Monitoring Network

- Partner collaboration and role of research institutions in national drug efficacy monitoring (Manuel Hetzel, Swiss Tropical Institute, Switzerland)
- Capacity-building, funding (Dorina Bustos, WHO Thailand)
- Work plan, communication and coordination of the Pacific Network (Lasse Vestergaard, WHO Philippines)

Session 5: Supportive Action

- Health research involving human subjects: ethical considerations and procedures to follow (Manju Rani, WHO WPRO)
- Implementation of quality assurance for malaria microscopy in TES (Dorina Bustos, WHO Thailand)
- Operational research to enhance drug efficacy monitoring, prevent drug resistance and optimize treatment for malaria (Lasse Vestergaard, WHO Philippines)