Meeting report of the expanded Bangladesh, Bhutan, India, Nepal, Sri Lanka (BBINS) Malaria Drug Resistance Monitoring Network

New Delhi, India

28–29 August 2018
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Abbreviations

ACT  artemisinin-based combination therapy
AL  artemether–lumefantrine
AS  artesunate
BBINS  Bangladesh, Bhutan, India, Nepal, Sri Lanka
CDS  Communicable Diseases Department
CQ  chloroquine
DHA  dihydroartemisinin
ECA  external competency assessment
FDMN  Forum Dialogu Miedzy Narodami
GMP  Global Malaria Programme
GMS  Greater Mekong Subregion
GTS  Global Technical Strategy
HANMAT  Horn of Africa Network for Monitoring Antimalarial Treatment
iDES  integrated Drug Efficacy Surveillance
K13  Kelch 13
MoH  Ministry of Health
MoHFW  Ministry of Health and Family Welfare
MQ  mefloquine
NIMR  National Institute of Malaria Research
NIRTH  National Institute for Research In Tribal Health
NMCP  National Malaria Control Programme
NSP  National Strategic Plan
NVBDCP  National Vector Borne Disease Control Programme
PCD  passive case detection
PCR  polymerase chain reaction
PIP  piperaquine
PQ  primaquine
QA  quality assurance
QC  quality control
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
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<tr>
<td>SP</td>
<td>sulfadoxine–pyrimethamine</td>
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<tr>
<td>TES</td>
<td>therapeutic efficacy studies</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Summary

The third meeting of the Expanded Bangladesh, Bhutan, India, Nepal, Sri Lanka (BBINS) Malaria Drug Resistance Monitoring Network was convened in New Delhi, India on 28–29 August 2018. Apart from the BBINS countries, the meeting was also attended by Maldives, Indonesia and Timor-Leste. The meeting provided an update on the recommendations of the 2016 Meeting and shared the results of the recent therapeutic efficacy studies (TES) or integrated drug efficacy surveillance (iDES) in these countries. Updates on molecular marker Kelch 13 (K13) for tracking artemisinin resistance and other molecular markers for malaria drug resistance were also shared. The countries developed workplans and budgets for TES monitoring in 2019–2020. Discussions were also held on possible harmonization of future malaria treatment regimens across countries.

Conclusions

- Most countries in the region have shown a decline in malaria cases.
- All countries except Maldives, have recently updated their National Treatment Guidelines (NTGs).
- The first-line treatment in all countries is currently working for both *P. falciparum* and *P. vivax* malaria.
- The second line treatment in some countries has not been defined. Some of them are based on quinine, which may not be the best option.
- K13 mutation related to partial artemisinin resistance has not been identified in the countries that have tested it, i.e. Bangladesh, India, Indonesia and Nepal.
- Four out of eight countries are unable to conduct TES due to the small number of cases and have moved/are moving to iDES.
- iDES has evolved as a method to conduct monitoring of malaria drug efficacy in countries/regions/areas with small numbers of malaria cases and malaria-free countries, as part of malaria elimination activities.
1 Introduction

1.1 Background

Monitoring anti-malarial drug resistance is an important activity of the national malaria programmes, as it ensures that malaria treatment policies being implemented are evidence-based, and that early deterioration in the efficacy of recommended treatment regimens is identified in a timely fashion and drug policy recommendations updated.

In the South-East Asia (SEA) Region, antimalarial drug resistance monitoring has been strengthened through the establishment of several drug resistance monitoring networks. The Bangladesh, Bhutan, India, Nepal, Sri Lanka (BBINS) network includes the countries named therein. Myanmar and Thailand are part of the Greater Mekong Subregion (GMS) network; and Indonesia and Timor-Leste are included in the Pacific Network.

The third meeting of the Expanded BBINS Malaria Drug Resistance Monitoring Network was convened in New Delhi, India on 28–29 August 2018. The meeting aimed to bring together the participants of the BBINS network in addition to three countries – Indonesia and Timor Leste from the Pacific network, and Maldives. This meeting provided an opportunity to follow up on the recommendations of the 2016 meeting, update the results of the recent therapeutic efficacy studies (TES) in these countries and the integrated drug efficacy surveillance (iDES), and also to develop workplans for such studies in the next two years.

1.2 Objectives

The objectives were to:

- provide an update on the recommendations of the 2016 Meeting;

- review and discuss implementation and results of the recent TES of each country;
• present updates on the iDES in near-elimination areas, and updates on the role and results of the molecular marker for tracking artemisinin resistance Kelch 13 (K13) and of other molecular markers for malaria drug resistance; and
• develop workplans and budgets for each country and the network for TES monitoring in 2019–2020, considering a possible harmonization of future malaria treatment regimens across countries.

2 Proceedings

2.1 Opening session

Dr Swarup Sarkar, Director, Communicable Diseases Department (CDS), WHO Regional Office for SEA delivered the speech on behalf of Dr Poonam Khetrapal Singh, Regional Director, WHO SEA Region. He mentioned that the SEA Region has embarked on an effort to eliminate malaria by 2030. There has been enormous progress in fighting the disease. Between 2010 and 2016, malaria deaths in the Region have declined by 60%. Maldives and Sri Lanka have already been declared malaria-free, and three other countries have the potential to eliminate malaria by 2020.

However, malaria remains endemic in nine of the 11 countries in the Region. Today, we confront the threat of multidrug resistance. This problem is especially acute in the GMS, and all of us are concerned about the risk that resistance could spread beyond the Subregion. Containing this threat is a major public health priority – not only for the SEA Region but for the entire world.

To confront the challenge of drug resistance, all countries in the Region now prioritize malaria drug efficacy monitoring as a core public health activity. This meeting brought together the five countries of the BBINS network with the goal of supporting high quality antimalarial drug efficacy monitoring in each country, fostering cross-border activities for drug surveillance and exploring the possibility of moving to a harmonized treatment regimen across the network.
Also joining this meeting were Maldives, which has been malaria-free since 1984, Indonesia and Timor-Leste.

Harmonization of treatment regimens across borders can help in ensuring treatment continuity for people on the move and facilitate joint procurement, which can lower prices and support uninterrupted treatment access, with particular benefits for small countries.

The meeting would jointly review the malaria drug resistance situation in member countries, share the results of recent monitoring efforts and best practices, discuss challenges, plan activities for the next two years and define the needs and expectations for the network.

He concluded by stressing the need to strengthen this collaborative approach with respect to drug efficacy monitoring. This would help to make a concrete contribution to the long-term health and well-being of the people in this Region and make SEA Region malaria-free once and for all.

In his remarks, Dr Sarkar mentioned that India contributed to about 75% cases of the Region. The Region has done well over the past few years. Maldives and Sri Lanka have eliminated malaria. The goal should be to eliminate malaria before antimalarial drug resistance sets in. He hoped that other countries would also intensify their efforts to eliminate malaria. It had been observed that countries which eliminated malaria recorded higher economic growth. This meeting was an important step towards the efforts of the Region to eliminate malaria.

Dr Pascal Ringwald was happy with the progress of the BBINS network. He mentioned that the Region has three types of countries: those conducting TES, countries targeting elimination and countries which have already eliminated malaria. Countries with few cases can opt for iDES for drug efficacy monitoring.

Dr P.K. Sen welcomed all participants on behalf of the National Vector Borne Disease Control Programme (NVBDCP) and Ministry of Health and Family Welfare (MoHFW). There had been tremendous progress in India with regard to malaria control, as was shown by the declining incidence. However, there is the threat of artemisinin resistance from the GMS. Chloroquine (CQ) was introduced in the 1940s and resistance to the drug developed in about 20 years. Artemisinin resistance was also knocking on the door. India generates data on drug resistance by conducting in vivo and in vitro studies as well as molecular marker assays.
There is a need to strengthen cross-border cooperation by information sharing and collaboration for malaria control activities. The BBINS+ network has played an important role in drug efficacy monitoring in the Region.

Dr N.S. Dharmashaktu reiterated the success in reducing malaria cases and that India was reporting less than 1 million cases annually. India is diverse in terms of vector diversity, parasite diversity, genetic variation, etc. There are better tools available for diagnosis, treatment and vector control. There is a need to use these tools effectively.

After self-introductions, Dr P.K. Sen and Mr Shishir Pant were appointed as Chair and Co-chair, respectively. Dr Din Syafruddin was appointed as rapporteur. Dr Eva Maria Christophel presented the objectives of the meeting.

2.2  Session 1 – updates

2.2.1  Updates on antimalarial drug resistance, including partial resistance to artemisinin and partner drugs

Dr Pascal Ringwald, Coordinator, Drug Efficacy and Response, WHO Global Malaria Programme gave a brief update on antimalarial drug resistance. He started his presentation with definitions of antimalarial drug resistance, artemisinin resistance, multidrug resistance and treatment failure. Artemisinin is the main compound present in all of the artemisinin-based combination therapy (ACT) treatments of uncomplicated as well as complicated malaria, with the peroxide bridge as the component common to artemisinin, sodium artesunate, artemether and dihydroartemisinin. The artemisinin derivative potentiates the activity of the partner drug. Hence, even if the efficacy of the partner drug is decreasing, it is masked by artemisinin and the combination is effective. Thus, the clinical outcome after ACT treatment depends on the sensitivity pattern of each component. Dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) have a strong correlation with sulfadoxine-pyrimethamine (SP) resistance. There are six K13 mutations validated for artemisinin resistance. Plasmeptin copy number has been associated with piperaquine (PIP) resistance. Molecular markers are yet to be validated for lumefantrine and amodiaquine resistance. There is high prevalence of C580Y mutation in eastern GMS. It has also been reported from
Africa and South America. Thus, molecular markers can give an indication of drug resistance and play a role in monitoring for it.

Dr Ringwald stated that owing to malaria elimination efforts, there were very few cases of *P. falciparum* malaria along the Thai–Myanmar border in 2015–2016, reducing the potential for spread to other regions.

ACTs are increasingly failing in the GMS. Artemisinin resistance has emerged independently in multiple geographic areas within the GMS, raising concerns about the effectiveness of a “firewall approach”.

There is need for an urgent and continued intensive regional malaria elimination campaign. Surveillance for artemisinin and partner drug resistance needs to be continued and strengthened in the GMS. Where surveillance signals a potential threat to leading ACTs, effective alternative ACTs should be identified and implemented before resistance reaches critical levels.

### 2.2.2 Updates on different drug efficacy surveillance systems: routine TES, iDES in the context of malaria elimination and importation

Dr Pascal Ringwald talked about the different drug efficacy surveillance systems like routine TES (in high burden areas) and integrated iDES in the context of malaria elimination and importation. The standardized protocol to monitor drug efficacy was reviewed. TES remain the gold standard for monitoring drug efficacy and informing treatment policy. These have been designed for efficacy monitoring of the recommended first- and second line drugs against both uncomplicated *P. falciparum* and *P. vivax* malaria, as well as any drug that needs to be tested prior to possible introduction into the treatment policy.

TES are conducted at sentinel sites. A sentinel surveillance system is used when high-quality data are needed that cannot be obtained through an existing routine surveillance system of data collection. Repeated TES in a limited number of sites is adequate to collect consistent longitudinal data and document trends. Depending on the malaria endemicity, a sentinel site could be a single health centre, a group of health centres in the same city/district or several
districts or even in cross-border health centres in two neighboring countries. The TES protocol can also be adapted according to transmission settings by modifying the inclusion criteria.

In very low transmission areas pursuing malaria elimination, the numbers of malaria cases are most often too low for the needed number of cases to be reached at sentinel sites. In such areas, the surveillance system is strengthened, and this can be used to also collect and analyse data on drug efficacy. In such areas, efficacy monitoring is shifted from using a sentinel surveillance system to relying on data collected via routine surveillance systems.

Integrating drug efficacy monitoring into the surveillance system can be done to ensure that the data collected on all malaria cases in the routine surveillance system can and are being used to also generate information about drug efficacy. Shifting from a sentinel surveillance system to relying on data from routine systems needs a strong and functioning surveillance system. The system should be able to report detected cases of malaria from both public and private health systems, provide supervised treatment and follow up of patients.

The shift to relying on data from routine systems typically only happens when there are too few cases to have a functioning sentinel surveillance system, and when the resources available allows for monitoring of the remaining cases.

Dr Ringwald stressed on the need to continually analyse the data, focusing on treatment failures and programmatic issues like lost to follow-up, and on the use of second line drugs in treatment failures. In addition to the continued analysis, it is necessary to define the time point when data is to be reviewed and discussed with World Health Organization (WHO).

2.2.3 Updates on progress and challenges towards malaria elimination in the SEA Region

Dr Eva Maria Christophel, Regional Adviser Malaria, Department of Communicable Diseases, Regional Office for South-East Asia gave an update on the progress and challenges pertaining to malaria elimination in the SEA Region. She started her presentation with the global malaria situation. Africa contributed to more than 90% of the estimated malaria cases and deaths worldwide. WHO South-East Asia Region had an estimated 14.6 million cases,
of which about two thirds are due to *P. falciparum*. There has been a 60% decline in the reported number of deaths in the Region from 2010 to 2016.

The endorsement of the WHO Global Technical Strategy (GTS) for Malaria 2016–2030 by the World Health Assembly was also highlighted. The strategy sets ambitious goals of malaria elimination by 2030, based on an analysis of current trends as well as modelling, citing Maldives and Sri Lanka, the countries which have already eliminated malaria.

She talked about the SEA Region Joint Vision and Action Plan 2017–2030 towards a malaria-free SEA Region. This action plan is based on the GTS and defines the Regional targets and milestones, based on country national strategic plans (NSPs). It also calls for national oversight and regional progress monitoring for malaria elimination. She also reiterated the need for strong political commitment to a malaria-free Region by 2030. Further, there are global initiatives like E2020 for Bhutan, Nepal and Timor-Leste, 10+1 initiative for the 10 high-burden African countries plus India, financing initiatives, regional initiatives, global oversight and numerous partnerships and research initiatives on malaria and its elimination.

However, there are also many challenges to malaria elimination efforts. They include technical challenges like drug resistance, insecticide resistance, *P. vivax* malaria and its relapses and changing vector ecology; and programmatic challenges like commitment at all levels, human resources, financing, inaccessible areas, community involvement, migration, emergencies, etc.

There is need of cross-border collaboration both within the Region and beyond to achieve the goal of malaria elimination. There are also various TES networks like BBINS, Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT), Pacific network, the GMS network and RAVERDA which can help in such collaboration.

As a part of the follow-up action of the 2016 BBINS meeting, Dr Christophel mentioned that TES were ongoing in Bangladesh, India, Indonesia and Myanmar. Laboratory capacity had been strengthened by conducting external competency assessment (ECA) in most SEA Region countries. Implementation of quality assurance of molecular markers was ongoing. Alternative ACT regimens were being tested in the GMS countries and India, with TES ongoing in all sentinel sites. In Thailand, TES had been integrated with the surveillance system.
WHO regularly provides updates on artemisinin resistance in the GMS on its website. It also networks to coordinate, share information, provide technical support and facilitates cross-border information sharing. Network meetings were organized in 2017 and 2018. Technical support is being provided at all levels and is being led by Drs Ringwald and Bustos.

2.3 Session 2 – country presentations on recent TES/antimalarial drug efficacy surveillance

2.3.1 Bangladesh (Dr Abu Nayeem Md. Sohel)
Malaria is endemic in 13 districts of Bangladesh. In 2017, the country reported 29 247 cases and 13 deaths. There has been a 26% reduction in cases since 2015. There has been further reduction in 2018 with only 3843 cases being reported up to June (69% reduction compared to the first half of 2017). The Annual Parasite Index (API) was 1.64. *P. falciparum* contributes to about 80% of the total cases. The peak is observed during June–August.

The antimalarial drug policy was revised in 2016. The first-line drug is artemether–lumefantrine (AL) for *P. falciparum* and CQ for *P. vivax* malaria. Artesunate suppositories have also been introduced for severe malaria. Three TES studies were carried out in the year 2017. There were no failures in Laxmichari, Khagrachari, Kaptai and Rangamati sites; while Lama and Bandarban showed one early treatment failure (ETF) (in 7 enrolled cases). In 2018, two TES studies were being carried out.

TES have not identified failures to ACT nor are there K13 mutations. However, there is the risk of spread of antimalarial drug resistance due to the displaced population Forum Dialogu Miedzy Narodami (FDMN) from Myanmar in the south-east (Cox’s Bazar), hence monitoring is required in those areas. There are increasing challenges to TES due to the difficulty in getting the required number of cases, difficult terrain and migrant populations.

The national drug policy of Bangladesh recommends low dose primaquine (PQ) (0.25 mg/kg body weight) as gametocidal agent in falciparum malaria. It was informed that two artesunate suppositories have been prequalified.
2.3.2 *India* (Drs Neena Valecha and Pravin Bharti)

There has been a steady decline in malaria cases in India over the past few years. The antimalarial drug policy was last revised in 2013. The first-line drug is AL in north-eastern states and artesunate+SP (AS+SP) in the rest of the country for *P. falciparum*, and CQ for *P. vivax* malaria. All fever cases are investigated for malaria by microscopy or rapid diagnostic test (RDT). National Institute of Malaria Research (NIMR) and National Institute for Research in Tribal Health (NIRTH) are conducting TES studies in India. Twenty-six TES studies were carried out between 2015 and 2017. The overall efficacy of (AS+SP) was 94.4–100% in 2015, 98.5–100% in 2016 and 100% in 2017.

No mutations associated with confirmed artemisinin resistance were detected among samples amplified and sequenced for 53-2126 nucleotide position of K13 gene. However, four non-synonymous mutations, N121S, K189T, P441L and E605L and three synonymous mutation 119L, 165T and 343D were observed.

Thus, both ACTs (AS+SP) and AL continue to be efficacious in India and there is no evidence of artemisinin resistance to date. However, mutations of resistance to the partner medicine SP are worrying.

It was discussed that there was a need to follow uniform procedures for studies carried out by different organizations. NIMR can take the lead in bringing all such organizations together and develop a mechanism for quality assurance. Certain states with low endemicity can integrate drug efficacy surveillance and may think of introducing iDES.

2.3.3 *Indonesia* (Dr Din Syafruddin)

In Indonesia, 28% of the population is at risk of acquiring malaria. Malaria incidence has gradually decreased over the last 10 years, although there had been a marginal rise during the years 2016 and 2017. Papua province contributes to more than 80% of the malaria cases of Indonesia. The recommended first-line treatment for both *P. falciparum* and *P. vivax* malaria is dihydroartemisinin-piperaquine (DHA+PIP) for 3 days. Seven TES studies were carried out on DHA+PIP during 2015–2017.
Studies carried out in East Nusa Tenggara, North Sulawesi and North Mollucas showed 100% efficacy for DHA+PIP in both *P. falciparum* and *P. vivax* malaria.

During 2017–2018, the DHA+PIP efficacy was 97.9% in *P. falciparum* in Papua province. It was 100% in *P. vivax* at both Jambi and Papua sites. Five specimens showed co-infection of *P. vivax* and *P. knowlesi* by polymerase chain reaction (PCR) in Jambi.

DHA-PIP continues to be effective for treatment of falciparum as well as vivax malaria. There is no evidence of artemisinin resistance to date. Since there are a declining number of cases located in hard-to-reach areas, it was suggested to include confirmed cases irrespective of parasitaemia for future efficacy monitoring.

It was clarified that the second line regimen is quinine + doxycycline (quinine + azithromycin in pregnancy).

### 2.3.4 Nepal (Mr Shishir Pant)

Nepal has seen a 60% reduction in malaria cases since 2010, with only 1293 cases reported in the year 2017. *P. vivax* accounts for about 90% of the cases. More than half the cases in 2017 were imported. CQ continues to be used for vivax malaria while AL is recommended for falciparum malaria.

There are four TES sentinel sites in Nepal: Kanchanpur, Kailali, Dhanusha and Jhapa. Previous TES studies were carried out in 2013–2014, which showed 96% efficacy of AL. There was no reported K13 mutation in the study isolates. Since 2015, all the reported cases are being followed up. TES and other evidence-generating operational research should be continued for timely and successful elimination.

Due to the low prevalence of malaria, it is becoming increasingly difficult to get a sufficient number of cases. There is need for continued monitoring and supervision for antimalarial efficacy. There were focal outbreaks of *P. vivax* malaria in previously low-risk classified districts/village development committees (VDCs).
It was discussed that the second line drug for \( P. \) vivax could be DHA+PIP or artesunate (AS)+mefloquine (MQ). There are lesser numbers of \( P. \) falciparum cases reported, making the TES difficult. However, given 90% \( P. \) vivax predominance, CQ efficacy should be monitored. It was also discussed that the numbers shown are the reported numbers, and that actual numbers could be more. There was a need to generate data on cases from the private sector. The surveillance system has to be more robust as the number of cases decrease. Quality-assured RDT should be used for surveillance.

2.3.5 Bhutan (Mr Singye Dukpa, Mr Kesang Wangchuk)

Bhutan reported 62 cases in 2017 and most of them were \( P. \) vivax. More than three fourths of all cases were imported. CQ is recommended for vivax malaria, while AL is recommended for falciparum malaria. Directly observed therapy is given to confirmed malaria patients. There are challenges in implementing the routine national TES: very few malaria cases, unavailability of genotyping facility, migration, imported cases making follow-up difficult and lack of harmonized cross-border collaboration. ECA was organised in Bhutan recently and there are several WHO Level 1 and 2 microscopists. While Bhutan is on the verge of eliminating malaria with the support of WHO and the Global Fund, cross-border malaria remains a major threat to elimination.

It was discussed that the Government of India/NIMR can help in genotyping. It will be good if bordering districts from both India and Bhutan can upload their data and share the results in case of failures. A ministerial meeting of the SEA Region countries was held, highlighting the need for cross-border collaboration and information sharing. It was also clarified that subclinical cases should not be included in TES unless cases presented with very recent history of fever prior to consult.

2.3.6 Maldives (Dr Fathimath Nazla Rafeeg)

Maldives does not have indigenous cases of malaria. However, there was one imported case in 2017. The case originated from the Indian subcontinent. The programme is continuing the
integrated vector management activities, early diagnosis and complete treatment and good surveillance. Antimalarials are available in the country only through the national programme. Due to very few or almost no cases, Maldives faces challenges in procurement of antimalarials. For entomological surveillance, the country has trained and experienced entomologists.

It was discussed that malaria patients staying in the country should be followed until Day 42. However, other nationals may be followed on Day 2 or until they leave the country. The efforts behind the success in eliminating malaria were discussed. This was the result of political commitment at the highest level, hard work, a dedicated and active national programme and community participation.

2.3.7 Sri Lanka (Dr Dewanee Ranaweera, Dr Priyani Dharmawardena)

There have been no indigenous malaria cases in Sri Lanka since 2013. However, imported cases pose challenges for the national programme. The country is in the “prevention of re-introduction” stage. Antimalarials are available only in the public sector, and all patients are hospitalized and treated for at least 3 days. The recommended antimalarials for P. vivax and P. falciparum are CQ and AL, respectively.

Sri Lanka is continuing iDES since 2014. For prevention of reintroduction, there is a need to ensure that patients are completely cured. Since the patients are from different parts of the world, they might have different therapeutic responses to drugs. All the confirmed malaria cases are subjected to malaria microscopy at least daily until parasitaemia clears, and again on Days 7, 14, 21, 28 and 42. P. vivax and P. ovale cases are followed up for 1 year for possible relapses. A published study reported that during 2015–2016, there were 77 imported malaria cases – 54 Sri Lankans and 23 other nationals. Presence of all five species of malaria parasite was seen. The efficacy of CQ in non-falciparum malaria was 100%, while that of AL in falciparum malaria was 92.8%.

There were challenges in procurement of small quantities of antimalarials. WHO and other countries in the Region could facilitate this on certain occasions.
There were certain best practices such as presence of both the vertical campaign and a decentralized system with a countrywide network of regional offices for anti-malaria activities, review and guidance by a technical support group, a 24 h functional hotline for surveillance and home visits by staff to ensure rigorous follow up.

It was informed that RDTs are used for screening at ports of entry, and limited targeted entomological surveillance was being continued. Malaria case management services are provided free of cost by the government. iDES was first started by Sri Lanka. It requires huge resources and the right attitude of the work force to maintain the malaria-free status.

2.3.8 Timor-Leste (Mr Ismail Salvador da Costa Barreto)

There has been a significant decline in malaria cases in the country over the past decade. The first six months of 2018 saw only five cases being reported. The current recommended treatment for both *P. vivax* and *P. falciparum* is AL with single dose PQ. During 2017–2018, TES was conducted on 11 *P. falciparum* and three *P. vivax* patients. The efficacy was 100%.

While it is good news that cases are declining, TES is increasingly becoming difficult and alternative strategies will be required. Patient recruitment and follow up is often challenging due to difficult terrain. It will be good to have support from the network countries in the form of molecular methods and capacity building.

CQ was replaced by AL for treatment of vivax malaria on the basis of results of TES in 2013. The country qualifies for iDES, and this should replace TES. The surveillance system should be improved to march towards elimination. There is need of cross-border research since there are lot of cultural and socioeconomic activities at the border with Indonesia and Papua New Guinea, making it difficult to define imported versus indigenous cases.

2.4 Session 3 – Operational aspects

2.4.1 Quality control in TES: implementation challenges (Dr Maria Dorina Bustos)
WHO has a standard checklist for monitoring quality control (QC) in TES. Some countries have been visited by external QC monitors and have used this QC checklist. This enables getting of immediate documented feedback for improvement. QC monitoring can identify the errors to help improve the quality of data such as transcription errors in filling up the case report forms and consent process, the quality of slides and recording of microscopy results, availability and recording of the rescue treatment provided, calibration of equipment, etc.

While QC is essential in order to generate quality data, it is a challenging task. There are TES implementation challenges that could be in the form of selecting the study sites which will have the potential to recruit the appropriate number of patients, getting the protocol reviewed by the ethics committees, administrative delays in release of funds and registration of the trial with the appropriate clinical trials registry. During TES implementation, there is a need to strictly adhere to the protocol, obtain consent and/or assent as appropriate and ensure proper documentation including observed treatment. Regular supervisory visits by the principal investigator and medical monitor, especially in the initial phase, can help overcome such challenges. Obtaining consent for conducting the pregnancy test for females and minors of child-bearing potential may not be appropriate as per local cultures/customs. Thus, often female minors and unmarried women are excluded from the efficacy studies. The weekly follow ups of enrolled patients is a challenge in hard-to-reach areas, particularly during the rainy season.

For the laboratory component, parasitological assessment can be affected by poor slide preparation and staining. Mixed infections are often missed. Improper collection and volume of dried blood spot samples means that not enough DNA material is available for molecular assays. Timely assays for genotyping are also an important component of QC. There should be quality assurance (QA)/QC for all the molecular procedures like genotyping and molecular markers of drug resistance.

Data entry in the excel sheets needs attention as well, from ensuring that all fields are completed with double data entry and validation and recording of PCR results when available. The Ethics Committee approval validity is for one year; studies should thus not be continued beyond two transmission seasons. The practice of validating microscopy by PCR makes interpretation difficult and is not part of the TES protocol. Comparative trials for surveillance are not recommended.
It was discussed that only digital thermometers should be used for TES. Institut Pasteur Cambodia conducts QA for molecular procedures. There was some discussion regarding the ideal time for administration of PQ. This depends on the research question: If one wants to monitor the efficacy of CQ alone in vivax malaria, PQ may be delayed until Day 28. Administering PQ on Day 0 or 2 in falciparum study should not affect the results.

2.4.2 The role of K13, P14 and other molecular markers of resistance

(Dr Pascal Ringwald)

The role of molecular markers of resistance was discussed. Having molecular tools is an asset, as genotyping can help differentiate between recrudescence and reinfection during TES. There are molecular markers available for CQ, sulfadoxine-pyrimethamine (SP), PIP and MQ. Amodiaquine, lumefantrine and pyronaridine do not (yet) have the molecular markers for resistance. Treatment failures along with presence of molecular markers for that antimalarial drug confirm the drug resistance. The mere presence of a molecular marker is a predictor of future treatment failure. The study of markers for artemisinin resistance (K13) is a part of the TES, and dried blood spots collected on Day 0 can be used for this purpose. There is need to build capacity in the countries, since some countries do not allow export of biological specimens.

WHO is working towards the implementation of Nagoya Protocol on sharing the specimens for molecular sequencing. For QA/QC of molecular tools, there are WHO collaborating centres. Institut Pasteur Cambodia is a reference laboratory for this activity of molecular markers of drug resistance and genotyping, and countries in the Region can avail these in this facility.

While molecular markers can predict future treatment failure, they are not 100% correlated with drug resistance.
2.4.3 National malaria treatment regimens across BBINS – exploring harmonization of treatment regimens and regional procurement (Dr Klara Tisocki)

Certain malaria medicines are not readily available to all countries in the right quality and quantities when needed. Small countries, or countries which have eliminated malaria, need only small stocks. It is often difficult to find suppliers with the right quality product. Depending on the malaria species prevalent and the level of drug resistance, multiple products may be needed and some of them may have limited market availability.

In such a scenario, big countries like India could go for national procurement. Smaller countries could go for joint or pooled procurement across countries in the region. Procurement can also be outsourced and could be a WHO-reimbursable procurement or made through the Global Fund or another third-party procurement agency.

Inter-country/regional collaboration on procurement can ensure sustainable access when products are in short supply or difficult to source, strengthen negotiating power, enhance transparency through better information sharing and reduce information asymmetries, achieve better prices through the economies of scale and reduce high transaction costs by pooling skills and capacities.

This can be successful if there is a certain level of harmonization with regard to essential medicines’ lists or formularies, quality standards and medicines regulation requirements, procurement processes, procurement rules and regulations, etc. There are certain prerequisites for pooled procurement such as strong political commitment, accepted level of harmonization, price transparency, delegation or reliance on a national procurement agency or third party, effective communication and efficient financial management. Dr Tisocki also listed the current national malaria treatment guidelines and antimalarials included in the national list of essential medicines in BBINS countries.

Countries acknowledged the assistance provided by WHO as well as other countries in making the antimalarials available. It was suggested that WHO Regional Office for South-East Asia may maintain a buffer stock of antimalarials to be used for emergency needs by the Member States. Countries expressed the need to know the procurement source for
prequalified PQ. It was also advised that countries may think of alternative ACTs as second line therapy instead of quinine.

2.5 Session 4 – Planning 2019–2020 surveillance of antimalarial drug efficacy in BBINS+: country and BBINS network plans

Dr Maria Dorina Bustos introduced the participants to the group work, dividing the participants into two groups: TES and iDES groups. She reiterated certain aspects of TES while preparing the plans: TES site selection according to malaria prevalence, TES monitoring, refresher training for microscopy, availability of two microscopists at site with the third microscopist preferably WHO Level 1 certified, etc. Group 1 consisted of participants from Bangladesh, India, Indonesia and Nepal while Group 2 consisted of participants from Bhutan, Timor-Leste, Maldives and Sri Lanka. After the group work, the country plans and budget were then presented in the plenary with some discussions.

2.5.1 Bangladesh

In Bangladesh, TES will be implemented by the National Malaria Control Programme (NMCP)/Ministry of Health (MoH). The country is planning to have three TES studies each year. In 2019, the efficacy of CQ against *P. vivax* will be assessed at Kaptai, Rangamati; Chunarughat, Hobigonj (border with India); CQ and AL, respectively for *P. vivax* and *P. falciparum* at Ukhiya, Cox's Bazar (border with Myanmar). In 2020, AL will be tested for *P. falciparum* at Alikodom, Bandarban; Baghaichari, Rangamati and Dighinala, Khagrachari. The studies will be carried out during the malaria transmission season between May and September. If the sample size is insufficient during this period, the study will be extended and the area will be expanded to the adjacent subdistrict.

It was discussed that for determining K13 mutations, sequencing is also required apart from PCR.

2.5.2 India

In India, the TES will be implemented by NIMR and NIRTH in collaboration with the NVBDCP. Both institutes have the facilities for molecular investigations. The country plans to organize
a refresher training for microscopists. The country is planning to have 10 TES studies each year and also implement iDES in two low-endemic states. In 2019, the country plans to assess the efficacy of AS+SP in *P. falciparum* at seven sites (Alipurdwar/Purulia, West Bengal; Kalahandi, Odisha; Raigarh, Chhattisgarh; Singroli district, Madhya Pradesh; Dahaud/Surendra Nagar, Gujarat; Mahboob Nagar, Telngana and Dakshina Kannada, Karnataka). One AL study has been planned in South Tripura, Tripura. Two studies will be conducted for CQ in *P. vivax*. iDES will be piloted in Sikkim.

In 2020, the country plans to assess the efficacy of AS+SP against *P. falciparum* at six sites: Mayurbhanj, Odisha; West Singhbhum, Jharkhand; Chandrapur, Maharashtra; Udaipur district, Rajasthan; East Godawari and Andaman & Nicobar Islands. Two AL studies will be carried out in *P. falciparum* in Mumin, Mizoram and East Garo Hills, Meghalaya. Two studies have been planned for CQ against *P. vivax* in Nooh, Haryana and Kanyakumari (Nagercoil), Tamilnadu. iDES will be continued in Sikkim and introduced in Punjab state.

It was discussed that since Sri Lanka received malaria cases from Uttar Pradesh and Tamil Nadu of India, it will be relevant to conduct TES in these states as well. Investigators informed that the country has sufficient WHO certified Level 1 microscopists.

### 2.5.3 Indonesia

Indonesia is planning TES from January 2019 to December 2020 in Papua (Jayapura and Keerom districts) and East Nusatenggara (Belu and other districts at the border with East Timor). The sites were selected due to the moderate to high malaria incidence in the eastern parts of the country. Systematic surveillance is not in place in these areas and there had been reports of DHA–PIP treatment failure from these areas. In some cases, the source of infection was from across the border. Hence, the country plans to conduct the studies along its borders. Such bordering health centres receive patients of different nationalities, which have different first-line drugs (DHA-PIP in Indonesia and AL in Papua New Guinea).

### 2.5.4 Nepal

The country has planned three studies for assessing the efficacy of CQ in *P. vivax* in 2019. The sites are Danusa (Province 2), Kailali and Kanchanpur (Province 7) and Mugu or Bajora
(Province 6). Both Bajora and Mugu have malaria cases but are logistically difficult sites. The country plans to organize refresher training for microscopists.

2.5.5 Bhutan, Timor-Leste, Sri Lanka and Maldives

Bhutan and Timor Leste have low transmission of malaria and are aiming for zero indigenous cases. Sri Lanka and Maldives have zero indigenous cases and are aiming for prevention of reintroduction. There is no resistance to first-line drugs for all species.

These countries plan to implement (or are already implementing) iDES. All the confirmed malaria cases will be given directly observed therapy for the initial three days. Parasitological assessment will be done on Days 0, 3 and 28.

Facilities for molecular markers are not available in all the countries. In such cases, DNA extraction and molecular tests will be carried out at a specialized reference laboratory.

It was discussed that it is important for these countries to capture each and every case. Active as well as reactive case detection should be carried out. It will be good if Bangladesh, Bhutan and Nepal can collaborate with India, and Timor-Leste with Indonesia for molecular studies. However, it is for these countries to decide on how to integrate and coordinate their activities with the network.

3 Conclusions and recommendations

3.1 Conclusions

- Most countries in the Region have shown a decline in malaria cases.
- All countries except Maldives have recently updated their national treatment guidelines.
- First-line treatment in all countries is currently working for both *P. falciparum* and *P. vivax* malaria.
• Second line treatment in some countries has not been defined. Some of them use quinine, which may not be the best option.
• K13 mutation related to partial artemisinin resistance has not been identified in the countries who have tested for it, i.e. India, Bangladesh, Indonesia and Nepal.
• Four out of eight countries are unable to conduct TES due to the small number of cases and have moved/are moving to iDES.
• iDES has evolved as a method to conduct monitoring of malaria drug efficacy in countries/regions/areas with small numbers of malaria cases/malaria-free countries as part of the malaria programme’s malaria elimination activities.

3.2 Recommendations

3.2.1 Recommendations to countries: general

• Countries/areas with moderate to high transmission (Bangladesh, India, Indonesia and Nepal) should continue to implement high-quality TES for P. falciparum and P. vivax malaria, using standard WHO protocol.
• Countries/areas with low transmission pursuing elimination (Bhutan, Timor-Leste) or those which are malaria-free (Maldives, Sri Lanka) should continue or implement iDES integrated into their relevant programmes. This also applies to areas within other countries with low transmission.
• Cross-border collaboration for TES may be useful, depending on the programme and TES objectives (such as between Indonesia and Timor Leste), and could be an entry point for effective cross-border collaboration in general for malaria elimination.
• Unregulated use of antimalarials (including in the private sector) continues to fuel development of drug resistance and needs to be more stringently addressed from a health systems perspective as well as through malaria programmes.
• Countries should review their second line treatment regarding feasibility and potential to quickly replace the first-line treatment once it is failing.
3.2.2 Recommendations to countries: TES

- Training of the TES teams (central and local) should be ensured before commencing the studies.
- Malaria microscopy laboratory capacity should be strengthened in general to include refresher training and establishing national QA schemes, and in particular for the microscopists in the TES teams.
- Second line and alternative drugs should be tested before the first-line is failing to establish baseline information on potential alternative regimen.

3.2.3 Recommendations to countries: iDES

- iDES is part of elimination surveillance.
- Real-time and detailed surveillance information is critical.
- All patients/parasite carriers in the area should be included in iDES.
- The follow up needs to be continued to an endpoint: patient cure or patient leaving the country, while the details of the follow-up scheme need to be developed based on feasibilities in each country.

3.2.4 Recommendations regarding treatment harmonization and procurement

- As a number of countries face difficulties in procuring antimalarials, especially those with a small number of cases or only imported cases, support for procurement is required. Different options are possible (national, joint/pooled, outsourced) which need to be further pursued.

3.2.5 Recommendations to WHO/BBINS Network

- Given the dynamic malaria and drug resistance situation regionally and globally, and given the Region’s commitment to malaria elimination, information exchange is an important function of the network, which should be continued.
- Ways to share knowledge/experience/best practices on malaria elimination and drug efficacy monitoring between countries of the Region should be explored and facilitated, e.g. webpages, webinars.
- Support should be provided to countries on laboratory issues including:
  - continuing to strengthen malaria microscopy QA
o strengthening PCR analysis where relevant
o facilitating QA of molecular markers.

- Networking between laboratories should be facilitated. Regional reference laboratories should be defined and supported. WHO collaborating centres and the existing laboratory networks can play a role in this regard.
- Regional medicine procurement should be facilitated. Efforts should be made to update the inclusion of PQ and CQ in the WHO prequalification scheme.

4 Closing session

Dr Eva Maria Christophel closed the 2-day meeting, thanking the Chair, rapporteur, participants and all staff who helped make this meeting a success.
Annexure 1 – Programme of work

Meeting of the Expanded Bangladesh, Bhutan, India, Nepal, Sri Lanka (BBINS) Malaria Drug Resistance Monitoring Network

Metropolitan Hotel, New Delhi, India, 28-29 August 2018

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<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>08:00–08:30</td>
<td>Registration</td>
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<td>08:30–09:30</td>
<td><strong>Opening session</strong></td>
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<td><strong>MC welcomes the participants</strong></td>
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<td><strong>Welcome address</strong></td>
<td>WHO Regional Office for South-East Asia</td>
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<td><strong>Welcome message by WHO Regional Director for SEA</strong></td>
<td>WHO Regional Office for South-East Asia</td>
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<td><strong>Remarks</strong></td>
<td>WHO Global Malaria Programme</td>
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<tr>
<td>Time</td>
<td>Session 1: Updates</td>
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<tr>
<td>10:00–</td>
<td>Updates on antimalarial drug resistance, including partial resistance to artemisinin and partner drugs (45 mins presentation, 15 mins discussion)</td>
<td>Dr Pascal Ringwald, Coordinator, Drug Efficacy and Response, WHO Global Malaria Programme</td>
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<tr>
<td>11:00–</td>
<td>Updates on different drug efficacy surveillance systems: routine TES, integrated drug efficacy surveillance (iDES) in the context of malaria elimination and importation (45 mins presentation, 15 mins discussion)</td>
<td>Dr Pascal Ringwald</td>
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<td>12:00–</td>
<td>Updates on progress and challenges towards malaria elimination in the SEA Region, and review of recommendations of the previous Therapeutic Efficacy Studies (TES) network meeting (15 mins presentation, 10 mins discussion)</td>
<td>Dr Eva Maria Christophel, Regional Adviser Malaria, Department of Communicable Diseases, WHO Regional Office for South-East Asia</td>
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**Chairs Day 1: India, Maldives**

**Introduction of participants**

**Objectives of the meeting**

**WHO Regional Office for South-East Asia**

**WHO Global Malaria Programme**

**Coffee/tea break**
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<thead>
<tr>
<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>12:30–13:30</td>
<td>Lunch break</td>
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<tr>
<td>13:30–15:30</td>
<td><strong>Session 2:</strong> Country presentations on recent therapeutic efficacy studies/antimalarial drug efficacy surveillance</td>
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<td></td>
<td>Group 1: Countries conducting TES</td>
<td>TES Principal Investigator</td>
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<td>(15 mins presentation, followed by 15 mins discussion)</td>
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<tr>
<td></td>
<td>Bangladesh</td>
<td>TES Principal Investigator</td>
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<td>India</td>
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<td>Indonesia</td>
<td>TES Principal Investigator</td>
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<td>Nepal</td>
<td>TES principal Investigator</td>
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<td>15:30–16:00</td>
<td>Coffee/tea break</td>
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<td>16:00–16:40</td>
<td><strong>Group 2:</strong> Countries with &lt;100 confirmed malaria cases in 2016</td>
<td>Malaria Programme Officer</td>
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<td>(10 mins presentation, followed by 10 mins discussion)</td>
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<td>Bhutan</td>
<td>Malaria Programme Officer</td>
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<td>Timor Leste</td>
<td>Malaria Programme Officer</td>
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<td>16:40–17:20</td>
<td><strong>Group 3:</strong> Malaria-free countries in Prevention of Re-establishment of malaria (PoR)</td>
<td>Malaria Programme Officer</td>
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<td>(10 mins presentation, followed by 10 mins discussion)</td>
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<td>Maldives</td>
<td>Malaria Programme Officer</td>
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<td>Sri Lanka</td>
<td>Malaria Programme Officer</td>
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<tr>
<td>18:00–19:30</td>
<td>Reception dinner (hotel venue)</td>
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<tr>
<td>08:30–08:45</td>
<td><strong>Summary of Day 1 (to be discussed)</strong></td>
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<tr>
<td>08:45–09:15</td>
<td><strong>Session 3: Operational aspects</strong></td>
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<td><strong>Quality control in TES: implementation challenges</strong></td>
<td>Dr Maria Dorina Bustos</td>
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<td>(15 mins presentation, 15 mins discussion)</td>
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<tr>
<td>09:15–09:35</td>
<td><strong>The role of K13, P14 and other molecular markers of resistance</strong></td>
<td>Dr Pascal Ringwald</td>
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<td>(10 mins presentation, 10 mins discussion)</td>
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<tr>
<td>09:35–10:00</td>
<td><strong>National malaria treatment regimens across BBINS – exploring harmonization of treatment regimens and regional procurement</strong></td>
<td>Dr Klara Tisocki, Regional Adviser Pharmaceuticals, Department of Health Systems Development, WHO Regional Office for South-East Asia</td>
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<td>(15 mins presentation, 10 mins discussion)</td>
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<td>10:00-10:30</td>
<td><strong>Coffee/tea break</strong></td>
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<tr>
<td>10:30–11:00</td>
<td><strong>Session 4: Planning 2019–2020 surveillance of antimalarial drug efficacy in BBINS+: country and BBINS network plans (including budgets)</strong></td>
<td>Dr Maria Dorina Bustos</td>
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<td></td>
<td><strong>Introduction to planning and plenary discussion</strong></td>
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<tr>
<td>11:00–12:00</td>
<td><strong>Group work:</strong></td>
<td>Dr Maria Dorina Bustos and facilitators (WHO staff)</td>
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<tr>
<td>12:00–13:00</td>
<td>Lunch break</td>
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<tr>
<td>13:00–14:00</td>
<td>Group work continued</td>
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<tr>
<td>14:00-16:00</td>
<td><strong>Presentation of country and BBINS network plans and support needs in plenary</strong> (10 mins presentation, 5 mins discussion)</td>
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<td></td>
<td>Country TES principal investigators and/or malaria programme officers</td>
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**Group 1:**
- Bangladesh
- India
- Indonesia
- Nepal

**Group 2:**
- Bhutan
- Timor-Leste
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<tr>
<td><strong>Session 8:</strong></td>
<td><strong>Next steps and closing</strong></td>
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<td>16:30–</td>
<td>Partners’ comments</td>
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<td>16:45</td>
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<tr>
<td>16:45–</td>
<td>Conclusions and recommendations</td>
<td>Dr Eva Maria Christophel, Dr Pascal Ringwald</td>
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<td>17:15</td>
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<td>17:15 –</td>
<td>Closing session</td>
<td>Dr Swarup Sarkar, Director Communicable Diseases, WHO WHO Regional Office for South-East Asia</td>
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</table>
Annexure 2 – List of participants

**Bangladesh**

Dr Abu Nayeem Md. Sohel  
Evaluator  
M & PDC  
DGHS  
Mohakhali, Dhaka

**Bhutan**

Mr Singye Dukpa  
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Vector Borne Disease Control Program  
Ministry of Health  
Gelephu

Mr Kesang Wangchuk  
Lab Officer  
Vector Borne Disease Control Program  
Ministry of Health  
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Director  
NVBDCP  
Ministry of Health & Family Welfare  
Government of India  
New Delhi
Dr N.S. Dharmashaktu  
Principal Advisor (PH)  
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Ministry of Health & Family Welfare  
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Dr Neeraj Dhingra  
Additional Director  
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Jakarta

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Health Protection Agency
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Male
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Public Health Officer  
Epidemiology and Disease Control Division  
Ministry of Health and Population  
Kathmandu

Mr Shishir Pant  
Entomologist  
Vector Borne Disease Research and Training Centre  
Hetauda

**Sri Lanka**

Dr P. Dharmawardena  
Regional Malaria Officer  
Ministry of Health, Nutrition & Indigenous Medicine  
Government of the Democratic Socialist Republic of Sri Lanka  
Colombo

Dr D. Ranaweera  
Consultant Community Physician  
Anti-Malaria Campaign  
Ministry of Health, Nutrition & Indigenous Medicine  
Government of the Democratic Socialist Republic of Sri Lanka  
Colombo

**Timor-Leste**

Mr Ismail Salvador da Costa Barreto  
Executive Director
Laboratorio Nacional da Saude
Dili

Ms Jonia Lourenca Nuten Brites da Cruz
Pharmaceutical Officer
Department of Pharmacovigilance and Medicine Control
Ministry of Health
Dili

Partners

Dr Kamini N Mendis
Consultant
Colombo, Sri Lanka

WHO secretariat

Country offices

Dr Mya Ngon
Medical Officer
WCO Bangladesh

Dr Sonam Yangchen
National Professional Officer
WCO Bhutan

Dr Roop Kumari
Medical Officer
WCO India

Dr Lungten Wangchuk
Scientist
Communicable Diseases
WCO Nepal

Dr Subhash Lakhe
National Professional Officer
WCO Nepal

Dr Manjula N. Danansuriya
National Professional Officer
WCO Sri Lanka

WHO/HQ

Dr Pascal Ringwald
Coordinator
Drug Efficacy and Response
GMP

WHO Regional Office for South-East Asia

Dr Swarup Sarkar
Director Communicable Diseases

Dr Eva-Maria Christophel
Regional Advisor – Malaria

Dr Dorina Bustos
Technical Officer Malaria
WCO Thailand

Dr Risinha Gayan Premaratne
Technical Officer Malaria

Dr Klara Tisocki
Regional Advisor – Pharmaceuticals

Ms Susha Sreedharan
Administrative Assistant Malaria

Ms Naina Sethi
Administrative Assistant
Annexure 3 –
Country plans,
2019–2020

<table>
<thead>
<tr>
<th>Country</th>
<th>Name of site</th>
<th>Drug s to test</th>
<th>Proposed budget in US dollars</th>
<th>Drug s to test</th>
<th>Proposed budget in US dollars</th>
<th>Fundin g source</th>
<th>Implementor/s</th>
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<th>No.of Level 1 WHO certifie d expert s</th>
<th>TES Monito r</th>
<th>Monitori ng and supervis ion</th>
<th>Other needs/ gaps, capacit y buildin g</th>
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<tr>
<td>Bangladesh</td>
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<td>49 500</td>
<td>MoH/N MCP</td>
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<td>MT lab of UHC/MT lab of BracMR G</td>
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<td>UHFPO and CS, PI, Co-I</td>
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<td>Baghaich ari, Rangam ati</td>
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<td>Ukhiya, Cox's Bazar(</td>
<td>AL, CQ</td>
<td>Dighinala</td>
<td>AL</td>
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<td>Code</td>
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<td>Type</td>
<td>District</td>
<td>Ministry</td>
<td>Required</td>
<td>Pool of more than 20microscopists</td>
<td>Institute</td>
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**Indonesia**

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