In the Asia-Pacific region, the monitoring of the efficacy of antimalarial drugs including artemisinins and artemisinin-based combination therapies (ACTs) has become a routine activity of the national malaria programs using a standardized WHO therapeutic efficacy study (TES) protocol. It aims to identify early signs of resistance of recommended treatment regimens to drive evidence-based review and update of a country’s national drug policy.

The 4th Meeting of the BBINS Malaria Drug Resistance Monitoring Network (Bangladesh, Bhutan, India, Nepal and Sri Lanka) convened in New Delhi, India on 15–16 October 2019. The discussions highlighted the results of therapeutic efficacy studies including updates on molecular markers for drug resistance, showing that the 1st-line artemisinin-based combinations therapies (ACT) in all countries are currently effective against both P. falciparum and P. vivax malaria; countries to further strengthen malaria microscopy QA; and adopt iDES for monitoring of malaria drug efficacy in areas with low malaria cases as part of the programme’s elimination surveillance activities. Also discussed were workplans for continuing studies over the next two years.
The Meeting of the Bangladesh, Bhutan, India, Nepal, Sri Lanka (BBINS) Malaria Drug Resistance Monitoring Network

A Report

New Delhi, India, 15–16 October 2019
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<td>ACD</td>
<td>active case detection</td>
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<td>ACPR</td>
<td>adequate clinical and parasitological response</td>
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<td>ACT</td>
<td>artemisinin-based combination therapy</td>
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<td>AL</td>
<td>artemether-lumefantrine</td>
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<td>API</td>
<td>annual parasite incidence</td>
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<td>AS</td>
<td>artesunate</td>
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<td>BBINS</td>
<td>Bangladesh, Bhutan, India, Nepal, Sri Lanka</td>
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<tr>
<td>CDS</td>
<td>Communicable Diseases Department</td>
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<tr>
<td>CQ</td>
<td>chloroquine</td>
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<td>DHA</td>
<td>dihydroartemisinin</td>
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<td>ECA</td>
<td>external competency assessment</td>
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<td>ERC</td>
<td>Ethics Review Committee</td>
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<td>ETF</td>
<td>early treatment failure</td>
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<td>GMP</td>
<td>Global Malaria Programme</td>
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<td>GMS</td>
<td>Greater Mekong Subregion</td>
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<td>GTS</td>
<td>Global Technical Strategy</td>
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<td>ICF</td>
<td>informed consent forms</td>
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<td>iDES</td>
<td>integrated Drug Efficacy Surveillance</td>
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<td>K13</td>
<td>Kelch 13</td>
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<tr>
<td>LCF</td>
<td>late clinical failure</td>
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<tr>
<td>LPF</td>
<td>late parasitological failure</td>
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<td>MQ</td>
<td>mefloquine</td>
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<td>NMCP</td>
<td>National Malaria Control Programme</td>
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<td>NSP</td>
<td>National Strategic Plan</td>
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<td>NTG</td>
<td>National Treatment Guidelines</td>
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<td>NVBDCP</td>
<td>National Vector Borne Disease Control Programme</td>
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<td>PCD</td>
<td>passive case detection</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PIP</td>
<td>piperaquine</td>
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<tr>
<td>PQ</td>
<td>primaquine</td>
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<tr>
<td>QA</td>
<td>quality assurance</td>
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<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
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<tr>
<td>SEARO (WHO)</td>
<td>Regional Office for South-East Asia</td>
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<td>SP</td>
<td>sulfadoxine-pyrimethamine</td>
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<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

A meeting of the BBINS Malaria Drug Resistance Monitoring Network was convened in New Delhi, India on 15–16 October 2019. Country representatives from BBINS countries (Bangladesh, Bhutan, India, Nepal and Sri Lanka) and Maldives, country office focal points, experts and partners attended the meeting.

An update of the recommendations of the 2018 meeting, and results of recent therapeutic efficacy studies (TES) or integrated drug efficacy surveillance (iDES) in these countries were presented. Updates on molecular marker Kelch 13 (K13) for tracking resistance to artemisinin and other malaria drugs, were also shared.

The countries then developed workplans and budgets for TES monitoring in 2020–2021. Panel discussions were also held on updating malaria treatment regimens across countries, based on evidence generated from TES studies, and data on molecular markers for drug resistance.

The salient conclusions which emerged are:

1. Most countries in the Region have shown a decline in malaria cases;
2. First-line artemisinin-based combination therapies (ACTs) for both \textit{P. falciparum} and \textit{P. vivax} malaria, are currently effective in all countries;
3. K 13 mutations have been identified in the countries which have tested it, i.e., Bangladesh and India. However, these mutations are not resistance-confirmed mutations, and are not linked to clinical treatment failure. Countries have been advised to conduct further investigation on reports of K 13 mutations.
4. Considering the challenges for TES, especially due to decline in the number of cases for enrollment, the enrollment criteria and study area need to be suitably modified without compromising technical/ethical issues.
5. Countries should strengthen capacities for microscopy and ensure quality assurance (QA) for TES. The external competency assessment (ECA) for microscopists, should include technicians engaged in TES studies.
6. Results/reports of TES studies should be shared with the country programme soon after completion, and countries encouraged to publish the same in national/international journals.
7. WHO should support QA for polymerase chain reaction (PCR) and molecular markers.
8. Countries of the region, which are not part of the BBINS Network but share borders with it, should also be invited for TES meetings.
1. **Background**

Three Antimalarial Therapeutic Efficacy Monitoring Networks in the Asia-Pacific have played a leading role in supporting countries to implement quality monitoring in malaria drug efficacy.

The BBINS Network, the Pacific Network (covering Indonesia, Malaysia, Papua New Guinea, Philippines, Solomon Islands, the Democratic Republic of Timor-Leste and Vanuatu) and the Greater Mekong Subregion (GMS) Network (covering Cambodia, Lao People Democratic Republic, Myanmar, Thailand, Viet Nam and the Yunnan province of the People's Republic of China), have been in existence for several years now.

Network meetings have been organized everyone to two years. BBINS meetings were held in 2012, 2014 and 2018, while Pacific Network meetings were held in 2011, 2013, 2014 and 2019. Joint meetings of all three Networks were organized in 2015 and 2016.

These meetings were attended by representatives and principal investigators from the country malaria control programmes, WHO staff from all levels of the Organization, development partners, key collaborating technical institutions, partners and NGOs.

The Networks support national malaria programmes in developing and budgeting two-year country plans, conducting in vivo therapeutic efficacy studies (TES) of national first-line antimalarial drugs (and potential alternative regimes, if required), upon *P. falciparum* and *P. vivax* at selected sentinel sites.

In countries nearing elimination and with very few cases, like Bhutan and Nepal, and in those aiming for subnational elimination, iDES is the best approach to monitor drug efficacy. The Networks provide support to implement both TES and iDES, and quality-assured study drugs and clinical monitoring.

They also facilitate laboratory networking across the Region to cross-validate microscopy slide readings, assess and standardize molecular techniques differentiating recrudescence from reinfection, and the use of molecular markers for resistance and quality control.

This meeting contributed significantly to the South-East Asia Regional Director's Flagship Priority Programme to strengthen antimicrobial resistance surveillance. Countries are enabled to implement malaria strategic plans, with focus on improved diagnostic testing and treatment, antimalarial resistance monitoring surveillance, epidemic detection and response through capacity strengthening, and updated treatment policy recommendations and guidelines in keeping with the strategic direction set by the Global Malaria Programme (GMP).

2. **Objectives of the meeting were:**

   (1) Updating on the recommendations of the 2018 meeting;

   (2) Reviewing and discussing the implementation and results of recent TES in each country;
(3) Updating iDES in near-elimination areas, the role and results of Kelch 13, the molecular marker for tracking artemisinin resistance, and that of other molecular markers for malaria drug resistance;
(4) Developing work plans and budgets for each country and the Network, for TES and iDES monitoring in 2020–2021, in the light of a possible harmonization of future malaria treatment regimens across countries.

3. Proceedings

Opening session

Dr T.Y. Aditama, Acting Director of the Department of Communicable Diseases (CDS) at the WHO South-East Asia (SEA) Regional Office, delivered the inaugural address on behalf of Dr Poonam Khetrapal Singh, Regional Director of WHO South-East Asia.

Dr Neeraj Dhingra, Director of India’s National Vector Borne Disease Control Programme (NVBDCP) gave a welcome address on behalf of the Government of India.

Dr Neena Valecha, Regional Adviser for Malaria at the SEA Regional Office, articulated the objectives of the meeting and introduced the Chair and the Rapporteur.

4. Session 1: Technical updates

4.1 Updates on antimalarial drug resistance, artemisinin resistance

Dr Charlotte Rasmussen, Technical Officer, WHO Global Malaria Programme, gave a brief update on anti-malarial drug resistance and artemisinin resistance. She said that despite available antimalarials being highly efficacious, there are reasons to be concerned about *P. falciparum* resistance in the GMS. Drug resistance may make malaria treatment difficult in the GMS; it may spread from the GMS to other parts of the world with a higher malaria burden, or, developments seen in the GMS, could be repeated elsewhere. Drug resistance, one of the possible causes of treatment failure, can be confirmed and monitored with molecular techniques. Partial artemisinin resistance, which may have appeared in 2001, was reported from the GMS in 2008. Artemisinin resistance has been found to be associated with mutations in the *P. falciparum* Kelch 13 (K13) propeller domain.

It has implications for the treatment of severe malaria and for the selection of ACT partner drug resistance. Distribution of the key Kelch 13 mutations, C580Y and F4461, in the GMS in 2018 was noted. Piperaquine (PIP) resistance has spread through the region and is linked to massive drug pressure, Dr Rasmussen said.

The WHO clinical outcomes after ACT treatment according to sensitivity patterns of each component is described. Treatment failures resulted wherever there was high grade partner drug resistance, and even when sensitivity to artemisinin was present. Dr Rasmussen noted that partial resistance to artemisinin and resistance to the partner drug, result in a high rate of treatment failure.

A significant decrease in cases and deaths (2012–2019) was reported in GMS, while Kelch 13 mutations were reported outside Asia too; C580Y was detected in Guyana and Papua New Guinea. Analysis showed that the *P. falciparum* Kelch 13 C580Y variant arose on a single, Guyanese haplotypic background, and was not imported from South-East Asia.

However, recommended ACTs are showing high efficacy elsewhere in the world, Dr Rasmussen noted. Artemisinin partial resistance has been observed in Papua New Guinea.
Information on TES results, molecular markers and drug efficacy is available on WHO "threat maps", which can be easily accessed on http://apps.who.int/malaria/maps/threats/.

4.2 Regional updates and review of TES studies in BBINS

Dr Neena Valecha presented the regional updates and review of TES studies in BBINS.

Global trends showed a decline in the number of cases of malaria from 239 million in 2010, to 214 million in 2015. In 2017, there were 219 million cases globally, i.e., 20 million fewer than in 2010. The years 2015–2017 had registered a slightly upward, though minimal trend, despite an overall dip in cases. This suggests that progress had generally stalled, Dr Valecha said.

The WHO African Region still bears the largest burden of malaria morbidity (92%), followed by the WHO South-East Asia Region (5%). *P. vivax* is responsible for 37.2% cases of malaria in the SEA Region. India has the largest share (85%), followed by Indonesia (13.6%) in the SEA Region. The incidence rate (number of cases per 1000 population) for the Region declined appreciably from 2010–2017, whereas it has either remained flat or, in the case of the WHO Region of the Americas, has increased (largely due to Brazil, Nicaragua and Venezuela).

The SEA Region witnessed a decrease in total reported cases and deaths in 2010–2015 and 2015–2017. Around 70% of the globally-estimated cases, and 71% of global deaths, occur in 10 countries in sub-Saharan Africa and in India. The goals and timelines of WHO's Global Technical Strategy for Malaria (2016–2030) were presented.

Dr Valecha also outlined the 10+1 Initiative, an intensified effort by WHO to reduce malaria cases and deaths. High-burden to High-impact (HBHI), a targeted malaria response by the Organization, encompasses four key mutually reinforcing response elements. They are: political will to reduce malaria deaths, strategic information to drive impact, better guidance, policies and strategies and a coordinated malaria response.

Of 21 countries identified by WHO in 2016 as having the potential to eliminate malaria by 2020, certain countries, like the People's Republic of China, El Salvador, Malaysia and the Democratic Republic of Timor-Leste are close to elimination and have been reporting zero indigenous cases since 2017–2018.

A systematic review was conducted to identify historical occurrences of malaria resurgence, and all causes were categorised according to whether they were related to weakened malaria control programmes, increased potential for malaria transmission or technical obstacles like resistance. Resurgence followed general deterioration of control programmes in Bhutan and Indonesia, weakening of activities in Nepal, Sri Lanka and Thailand and insufficient funding and resources for vector control in India. Political and social unrest were the causes in Bangladesh, Myanmar and Sri Lanka.

The need of the hour is to have accurate and robust data, greater community surveillance, a focus on border regions, an involvement beyond the health sector alone and, commitments of national governments at the highest level: in the form of national malaria elimination committees, integration of malaria programmes into the health system, quality-assured diagnostics and significant domestic financing (Cohen et al. Malaria Journal 2012, 11:122).

Dr Valecha said that there is a need to put regional and sub-regional networks in place to monitor drug efficacy, since the development of insecticide and antimalarial drug resistance is a potential threat to malaria eradication.
TES are conducted regularly across the BBINS Network, except in countries where the number of *P. falciparum* cases is low, or, in countries which are malaria-free. Varying proportions of treatment failures have been observed in *P. falciparum* cases, but are not related to Kelch 13 mutations, while ACT efficacy is more than 95%. Mutations have been detected for sulfadoxine-pyrimethamine (SP), but AS-SP is still clinically effective.

Chloroquine (CQ) remains effective for *P. vivax* malaria. Treatment regimens in SEA Region countries except India, Indonesia, Thailand and Myanmar, use artemether-lumefantrine (AL) as the first-line treatment for *P. falciparum* and quinine as the second-line treatment. Single-dose primaquine (PQ) is added to prevent transmission. For severe malaria, intravenous artesunate followed by oral ACT, should be the standard practice.

Dr Valecha recapped the recommendations made at the 2018 meeting, including the continuation of high-quality TES using standard WHO protocol, in countries/areas with moderate to high transmission (Bangladesh, India, Indonesia, Nepal).

Training of TES teams, including QA schemes for microscopists, should be ensured. Low-transmission countries pursuing elimination (Bhutan and Timor-Leste), or, those which are malaria-free (Maldives and Sri Lanka) should continue with, or implement and integrate iDES into their relevant programmes, she said.

Countries should review feasibility of changing the second-line treatment and quickly replace the first-line, once it begins to fail. Concluding her presentation, Dr Valecha stressed that support should be provided to countries on laboratory issues, including on malaria microscopy quality assurance, strengthening PCR analysis and facilitating QA of molecular markers. Networking between laboratories should be facilitated. Regional reference laboratories should be defined and supported.

4.3 Different drug efficacy surveillance systems: routine TES, integrated drug efficacy surveillance (iDES) in the context of elimination, and importation

Dr Charlotte Rasmussen presented findings on the monitoring of drug efficacy in TES and iDES.

TES is the gold standard for monitoring drug efficacy i.e., to estimate the percentage of treatment failures, in order to inform treatment policy. However, countries with lower numbers of malaria cases, adopt integrated iDES.

Following standardized protocol, TES are designed for efficacy monitoring of first- and second-line drugs for both *P. falciparum* and *P. vivax*, and for any drug that needs to be monitored prior to possible introduction into the treatment policy. TES are conducted at sentinel sites, when high-quality data is needed, but cannot be obtained through an existing routine surveillance system. WHO recommends that TES are done at sentinel sites at least once every two years. Factors other than drug resistance, can result in the non-disappearance or, the reappearance of parasites.

These include poor quality drugs, a lack of adherence, drug interactions, co-morbidities, medical conditions, poor drug absorption and reinfection. Such factors can be managed by quality-assured drugs, supervised treatment, control of co-morbidities and genotyping. The TES protocol can be adapted to transmission settings (high, moderate, low and very low transmission), thus ensuring that a minimum sample size is reached for a sentinel site. The evaluation and interpretation of, and the subsequent response to TES results need to be carefully gauged on day 3, 28 or 42.
In very low transmission areas, the minimum sample size for TES is difficult to achieve, as is the planning of studies due to changing epidemiology. If elimination activities are implemented, data from the routine system may be used, Dr Rasmussen noted.

Elements of case management to eliminate malaria are: the early identification of suspected cases, quality-assured parasitological confirmation of malaria, appropriate treatment, supervision and documentation of treatment compliance and patient follow-up. The routine system can provide information on numbers, and the percentage of treatment failures. The system for collection of drug efficacy can be shifted from sentinel sites to an integrated drug efficacy surveillance system.

iDES require a strong surveillance and case management system. The minimum data required is: the best possible confirmation that the patient took the drugs; data for day 0 and the end-day and the end of follow-up with confirmed cure, or, the day of failure. In case of failure, another full follow-up period is needed. Additional data can be collected if needed and depending on available resources.

Supervised treatment and - in case of treatment failure, second-line treatment, is mandatory. Hospitalization during treatment is recommended. Follow-up for *P. falciparum* is mandatory for 28 or 42 days, and for *P. vivax*, 28 days and three months (eight months in North-East Asia, South Asia, Central America). The recommended period of follow-up for *P. falciparum* is 42 days or 56 days, and one year for *P. vivax*. For diagnosis, species identification by rapid diagnostic tests (RDT), and/or microscopy in clinically suspected cases and microscopy on the end day, are mandatory.

Similarly, assays for molecular markers for reinfection/ recrudescence and drug resistance markers, are mandatory. There is a need to continually monitor the numbers and percentages of treatment failures, and of additional data on molecular markers. Programmatic issues, like the supervision of treatment, the percentage lost to follow-up, and whether second-line treatment was given and treatment failures followed up, need to be resolved.

### 4.4 A brief overview of the TES protocol template

Dr Maria Dorina Bustos, Technical Officer, WHO South-East Asia Regional Office outlined the TES protocol template.

TES is the gold standard to monitor drug efficacy, in order to update drug policy. It is designed for *P. falciparum* and *P. vivax*, and all drugs, including CQ, are designed for 28-day and 42-day follow-up based on complete cure. It is widely adopted by health ministries, national malaria control programmes and research institutions.

The protocol template is reworked into a practical format. It needs approval from the national and WHO ethics committees. It can easily be adapted to meet local conditions, while still maintaining a standardized data management. The template is available on the WHO website.

Dr Bustos also highlighted the significance of informed consent forms (ICF) being in English and in the local language and stressed the importance of strict compliance with the protocol of WHO’s Ethics Review Committee (ERC) for approval. Issues like funds allocated for laboratory supplies not exceeding 10% of the total budget (as per SEARO Regional Review Committee (RRC) rules), and unnecessary administrative delays, were discussed.
5. **Session 2: Country presentations on TES**

5.1 **Bangladesh (Dr Nazrul Islam, National Malaria Elimination and ATD Control Programme)**

Dr Nazrul Islam presented malaria trends in Bangladesh from 2015–2019. A steady decline was noted between 2015 and 2018. There was a 74% decline in cases, and 22% in deaths during that period. Till August 2019, 10,871 cases and six deaths had been reported. Dr Islam pointed out that at the time of this Meeting, those figures were 47% higher than 2018, but 53% less than 2017.

The monthly trend of cases from 2010–2019 showed, that the maximum number of cases was reported in the period June–August. Citing the updated national malaria treatment policy, Dr Islam noted that diagnostic methods at different level of care have been specified: blood slide examination at the health facility level, and RDT in emergency situations, or for admitted patients and at field level.

The National Treatment Guidelines (NTG) for first-line treatment is AL for uncomplicated malaria, intravenous (IV) artemesunate (AS) for severe malaria and CQ+PQ for vivax malaria. G6PD deficiency testing is done before the administration of PQ. Second-line drugs are AS-amodiaquine, AS-MQ and DHA-PIP. Primaquine (PQ) is indicated in uncomplicated hyperparasitaemia, but contra-indicated in pregnant and lactating women, and infants below 6 months of age. Mixed infections are treated with AL and PQ for 14 days, and complicated malaria with injectable AS+PQ for 14 days. For severe malaria, treatment of choice is intravenous (IV) AS, followed by a full dose of ACT once oral medication is tolerated, or, oral quinine and tetracycline/doxycycline/clindamycin for 7 days.

Pre-referral treatment in all ages above six years, is intra-muscular (IM) AS and artemether or quinine, and AS suppository for patients under 6 years of age. In pregnant women (and women who are not pregnant), uncomplicated malaria is treated with ACT in all trimesters. Alternate treatment is seven days of quinine and clindamycin. Severe malaria in pregnancy is treated with IV AS in all trimesters.

Antimalarial drug resistance data from Bangladesh published up to June 2013, was reviewed. Published studies indicated varying levels of resistance to CQ, MQ and SP. Combination therapy of CQ and PQ has proven ineffective, and combinations of SP with either quinine or CQ, have also shown poor efficacy. Recent studies indicated that artemisinin derivatives, such as AS, remain highly efficacious in treating *P. falciparum* malaria. Available data suggests that artemisinins, quinine, doxycycline, MQ-AS and azithromycin-AS combination therapies remain efficacious in the treatment of *P. falciparum* malaria in Bangladesh.

TES studies in 2012, and in 2013–2014 showed 100% efficacy of AL at three sentinel sites. Three TES studies were also carried out in 2017. There were no failures at the Laxmichari, Khagrachori and Kaptai, Rangamati sites; while Lama, Bandarban showed one ETF (in 7 enrolled cases). In 2018, two TES studies were carried out. Therapeutic efficacy studies have not identified failures of ACT, nor are there Kelch 13 mutations, but the country is at risk of importation of ACT resistance, particularly due to displaced populations from Myanmar, relocated in endemic districts in the south-east (Cox’s Bazar).

Dr Islam highlighted the bottlenecks in meeting the required sample size, and in getting patients admitted in the hospitals. Current activities include the mapping of resistance through molecular surveillance and monitoring of the Kelch 13 gene, treatment
of artemisinin-resistant *P. falciparum* malaria by triple ACTs (AL-AQ, DHA-PPQ), and that of severe malaria by injection AS + injection quinine. TES needs to be continued routinely at permanent sites for the programme, and WHO's technical support is required.

### 5.2 India (Dr Avdhesh Kumar, National Director, NVBDCP)

The population of India is close to 1.31 billion, of which 68.86% lives in rural areas. There are 37 states with an average population of 36 million; 678 districts with an average population of 1.86 million; 25 308 public health centres (PHCs) for an average population of 52 000; 153 655 sub-centres for an average population of 8500 and 700 000 accredited social health activists (ASHA) nationwide serving an average pro rata population of 1000 per ASHA.

From "control", to "eradication" to the current "elimination", the malaria programme has seen many ups and downs since 1953. The present status provides an opportunity to eliminate malaria with available tools. There has been a 63% decline in total malaria cases, a 48% reduction in *P. falciparum* cases, a 52% reduction in *P. vivax* cases and a 75% reduction in deaths in 2018, as compared to 2015. A decline in malaria cases was also observed in seven north-eastern states from 2009 to 2018. In 2018, the total number of cases dropped by 79%, *P. falciparum* cases by 77% and deaths by 84%.

Dr Kumar noted that the same pattern of decline continued in 2019, with a decline of 29% in total malaria cases, 30% in *P. falciparum* cases and number of deaths. The analysis of district-wide API reveals that the number of districts with API < 1 has increased from 512 to 594; districts with API ≥ 1–2, decreased from 41 to 19, API ≥ 2–5 decreased from 44 to 19 in 2018; API ≥ 5–8 decreased from 15 to 8, and the number of districts with API > 10, decreased from 36 in 2015, to 8 in 2018.

The same pattern was observed in north-eastern states from 2009–2018. The total number of districts with an API < 1, has increased from 25 (29%) in 2009, to 82 (85%) in 2018. Similarly, there has been a decline in the number of districts affected, in all API categories.

The targets of malaria elimination include elimination in 15 low transmission states/union territories (UTs) in Category 1 (API < 1) by 2020; elimination in 11 moderately transmitting states (API 1–2) by 2022 and elimination from all states/UTs by 2027. By 2030, preventing the re-establishment of malaria will be encouraged to maintain malaria-free status across the nation.

Dr Kumar then presented India’s National Treatment Guidelines (NTG). Uncomplicated *P. vivax* malaria (including in pregnant women) is treated with CQ and PQ. uncomplicated *P. falciparum* malaria is treated with ACT: AL in the north-eastern states and AS-SP in rest of India. AL is not recommended in pregnant women in their first trimester, and in infants under five months.

Uncomplicated *P. falciparum* malaria in pregnant women in the first trimester is treated with quinine, and in the second and third trimesters, with AL or, AS-SP. Complicated malaria is to be treated with IV quinine or, IV artesunate, and with quinine with doxycycline or, clindamycin in pregnant women and children under eight years. The initial IV treatment is to be followed by full-course, age-specific ACT-AL, or, AS-SP for three days, and PQ as a single dose on the second day.

Dr Kumar then presented a summary of TES done in India from 2002–2017. TES for CQ carried out in seven states covering 10 districts (14 sites), showed 100% efficacy. Similarly, TES studies for AS-SP carried out in 16 states covering 34 districts (66 sites)
showed an overall efficacy of 80%–100%. TES studies for AL in north-eastern states, showed an efficacy of 96%–100%.

There were issues and challenges in conducting TES. Since the north-eastern states border Myanmar, the question of whether to include the states in the GMS network, was discussed. There was debate also on the need to increase or decrease the number of sentinel sites with adequate sample sizes, for a large country like India. The frequency of TES at the same sites at intervals of two years, was also deliberated.

Finally, there was discussion on whether microscopy or PCR ought to be the standard diagnostic test.

5.3 India (Dr Praveen K. Bharti, Scientist-E, NIRTH and Dr Kuldeep Singh, Scientist-B & Officer-in-charge, ICMR-NIMR)

The malaria burden in India is disproportionate in tribal states, with Odisha in the east contributing some 15.4% of malaria cases, despite being home to only 3.5% of India’s total population. Chhattisgarh, with 2.7% of the overall population, contributes 18.3% of all cases, followed by Jharkhand, which accounts for 13.3% of all cases (2018). In total, about 11 states constituting 69% of the country’s population bear 95.8% of India’s total malaria cases.

Dr Kuldeep Singh described the TES activity for AL carried out by the Indian Council of Medical Research’s National Institute of Malaria Research (ICMR-NIMR), in collaboration with the National Vector Borne Disease Control Programme (NVBDPC) in the country’s north-eastern states in 2015–2017. In 2015, Meghalaya, Tripura and Mizoram showed 100% efficacy. In 2016, Tripura and Mizoram showed 100%, while Meghalaya showed 98.6%. In 2017 and though the sample size was inadequate, TES studies in Arunachal Pradesh, showed 100%, as did Mizoram.

TES studies for AS-SP carried out in the states of Madhya Pradesh (2015–2017), Gujarat (2015), Maharashtra (2015 and 2017), Jharkhand, West Bengal, Odisha, Chhattisgarh and Karnataka (2015 and 2016) showed 100% efficacy. TES studies carried out in 2015–2017 for CQ in Uttar Pradesh, Arunachal Pradesh, Karnataka and West Bengal showed 100% efficacy.

Indian isolates of P. falciparum were also frequently found to carry mutations in the genes that code for the targets of sulfadoxine and pyrimethamine: dihydropteroate synthase (dhps) and dihydrofolate reductase (dhfr) respectively. Mutation in P. falciparum dhfr enzyme gives rise to the highest level of pyrimethamine resistance, leading to treatment failures. In 2015, 2% were of the wild type, whereas 98% were mutants (18% single mutation and 80% double mutation) in other states of India.

In 2016–2017, 15% were wild type and 85% were mutants. From 2015–2017, triple mutation in north-eastern states increased to almost 40% while 98% were mutants and 2% were wild type. In the case of dhps mutations, the 2015–2017 trend showed that initially, 75% were wild type and 25% were mutants in 2015 and increased to 70%–80% mutants in 2017. In north-eastern states, 80% were mutants in 2015, and increased to 85% in 2017.

Pfcrtr mutations were observed in 100% samples of north-eastern states with AL treatment, and from the other sites with AS+SP treatment. The results corroborated the presently available data on the key CQ resistance mutation K76T; wherein very few samples carrying the wild type allele have been reported across different malaria endemic regions. Among Pfmdr1 gene mutations in three codons (N86Y, Y184F and D124Y) studied among the north-eastern sites, the majority was of the wild type, except in the states of Tripura,
Mizoram and Arunachal Pradesh, where 60%–100% mutations were observed in D124Y and N86Y.

TES studies carried out in 2014–2015 by ICMR-National Institute of Research in Tribal Health (NIRTH) for AS+SP in Jhabua, Janakpur, Koria and Simdega, showed 100% efficacy, whereas in Balaghat and Jagdalpur, efficacy was found to be 99%.

Madhya Pradesh is a highly endemic state in the country, constituting 7% of its total malaria cases, with more than 50% being *P. falciparum* infections.

In the study conducted by ICMR-NIRTH in Jabalpur, the therapeutic efficacy of ACT was assessed. Out of the total 1616 febrile patients screened (638 *P. falciparum* infections, 55 *P. vivax* infections, 25 mixed infections and 898 negative), 311 eligible patients with *P. falciparum* infection were enrolled.

Therapeutic efficacy of ACT was determined in 237 patients over the three-year period, by the in vivo method using a 28-day follow-up. Most of the patients showed adequate clinical and parasitological response (99.6%) with late parasitological failure (LPF) of 0.4%.


Therapeutic efficacy of AL was assessed. Out of the total 10 712 febrile patients screened (1602 *P. falciparum*, 224 *P. vivax*, 4 *P. malariae*, 1 *P. ovale*, 86 mixed infections and 8795 negative), 376 eligible patients with *P. falciparum* infection were enrolled. Therapeutic efficacy of ACT was determined in 356 patients over the three-year period. Efficacy was determined by the 28-day in vivo method. Most of the patients showed adequate clinical and parasitological response (98.9%), with LPF of 1.1%.

The spread of a *P. falciparum*-resistant strain has led to a significant resurgence of malaria morbidity and mortality. The cornerstone of malaria treatment in India from 2010 to present, is the ACT AS-SP for the treatment of uncomplicated *P. falciparum* malaria.

In a study conducted in Madhya Pradesh, central India, molecular genotyping of dihydrofolate reductase (dhfr), dihydropteroate synthase (dhps) and Kelch13 genes was analyzed. Msp-1 and msp-2 genotyping was used to differentiate recrudescence.

Molecular study revealed that 72% parasites were of the mutant genotype (27.2% single mutants, 43.5% double mutants and 1.3% triple mutants) for *pfhfr*, while *pfhps* showed 78.2% wild type alleles, and 21.8% mutants (18.1% single mutants and 3.7% double mutants).

Analysis of all samples revealed mutation in the K13 gene, along with non-synonymous single mutation at codon M579T (1.5%), and double mutations at codons M579T & N657H in 37%.

ACT remains effective for the treatment of uncomplicated *P. falciparum* malaria in Madhya Pradesh. However, increasing mutation in *pfhfr* (particularly triple mutations) and *pfhps*, may reduce susceptibility to partner drug SP and mutation in the K13 propeller gene, thus highlighting the need for continuous monitoring of the efficacy of ACT.

Prevalence of mutations linked to antimalarial resistance in *P. falciparum* was also evaluated in Chhattisgarh in central India. A total of 163 *P. falciparum* samples were successfully amplified and analysed for both the *pfhfr* and *pfhps* genes.
Out of the five pfdhfr codon mutations (A16V, N51I, C59R, S108N/T and I164l) conferring pyrimethamine resistance, only two, C59R and S108N, were found in this study, either as single mutants or in the form of a double mutant.

Only 22% of samples was found to be of the wild-type genotype. The majority (76%, n=124) of samples were double mutants and only 2% (n=3) of samples were single mutants. A total of 4 haplotypes were determined, with haplotype diversity of 0.375.

Out of the five pfdhps mutations (S436F/A, A437G, K540E, A581G AND A613 S/T) known to be involved in sulphadoxine resistance, three codons, S436A, A437G and K540E, were found to be mutant either as single, or double mutants. A low level (6%) of mutant genotypes (3% single and 3% double mutant) and a total of 3 haplotypes, were found with 0.106 haplotype diversity.

Ongoing TES activity in India for the year 2018–19 is being carried out at a total of 9 sites, out of which ICMR-NIRTH will evaluate 6 sites (Kokrajhar, Malda town, Udalgiri, South Garo Hills, Churachandpur and Lunglai), and ICMR-NIMR will evaluate 3 sites (West Garo Hills, Udalgiri and Dhala).

The current scenario (2015–2019) in India shows a decline in total malaria cases in all north-eastern states (Meghalaya, Tripura, Mizoram, West Bengal and Manipur), except Assam.

Field work on perennial malaria transmission has been completed at the Udalguri site in Assam. A total of 87 patients were enrolled for a therapeutic efficacy study, of whom 84 completed the follow-up. Efficacy was found to be 96.5%.

Out of 2161 patients screened in West Garo Hills, 13 were enrolled and all 13 completed the follow-up. Therapeutic efficacy was found to be 100%.

In Chawangte and Lawngtlai, out of 85 patients enrolled, 83 patients completed the follow-up. Efficacy was found to be 98%. In Dhalai, Tripura, 84 of 87 enrolled patients completed follow up and efficacy was found to be 96.5%.

A site in the district of North 24-Parganas in the state of West Bengal, was included for TES. However and since it did not report any Pf malaria, the additional site of Malda district has now been included. Only one patient was enrolled in Malda and there was no treatment failure. This study is in progress.

Similarly and since no Pf cases were found at the Kokrajhar site, the Udalgiri site was included. Out of 32 patients enrolled, 18 completed the treatment course with no treatment failure recorded. The follow-up is in progress for 14 patients.

In Churachandpur, very low incidence of fever cases was observed. No malaria cases were reported in Manipur in 2018 and till 2019. Therefore, study site Mizoram was included to meet the requisite number of the patient enrolment criteria.

In Lunglei, 16 out of 82 enrolled patients were completely followed-up, while the follow-up of 60 patients is in process. So far, no treatment failure has been recorded.

TES activities to be initiated in Indian states/UTs and districts by NIRTH, Jabalpur and NIMR, Delhi will include Udaipur, Dahod, Singrauli, Alipurduar, Midnapur, Raigarh, Mahboobnagar, Kalahandi and Dakshina Kannada.

Challenges faced during the studies include obtaining consent/assent/informed consent from subjects and authorities, co-operation from state governments, difficult
terrain, insurgency-related inaccessibility to areas, poor health infrastructure, compliance to the 28-day follow-up of patients, quality of microscopy and limited mobile network and public transport.

6. Session 3. Country presentations on iDES

6.1 Bhutan (Mr Singay Dukpa, Laboratory Officer, VDCP)

From 2020 to 2018, Bhutan reported a gradual decline in cases from 448 to 54, most of which are now imported. There was one death each in 2017 and 2018. From January to September 2019, there were 29 cases which were predominantly *P. vivax* (70%). Out of 54 reported cases in 2018, six were indigenous, while all others were imported. Twenty-four of these cases completed follow-up with no treatment failures. All other imported cases could not be followed up. There are three districts with low risk malaria transmission, bordering Assam and West Bengal in India.

The current NTGs recommend AL for *P. falciparum* and CQ+PQ for 14 days for *P. vivax*, with 3-day hospitalization for supervised treatment. The programme plans to review its treatment policy in 2020 and to introduce guidelines for chemoprevention, for imported labourers (non-Bhutanese working and residing in Bhutan).

A national reference laboratory (NRL) has been established for microscopy QA in Thimpu, although genotyping technical support and regular microscopy refresher training are still needed. Another major challenge is unrestricted movement across borders. With no treatment failures now, Bhutan is on the verge of eliminating malaria with the support of WHO and the Global Fund, hence pro-active cross-border collaboration is urgently needed.

6.2 Maldives (Ms Aishath Jaleela, Director, Pharmaceuticals, Food and Drug Authority)

Maldives is malaria-free since 1984, and vector-free since 1997. However, malaria importation remains a significant threat. Diagnosis of malaria is being done mainly by using RDTs. Microscopy for diagnosis is limited, due to quality issues. Introducing PCR-based diagnosis is under discussion and will be used. Any new case is immediately reported, thoroughly investigated, classified, radically treated, and entered into a central database. The treatment of cases depends on the source of infection. All ports of entry to the country are constantly monitored, and the ministry of health keeps a central stock of antimalarial drugs and public health insecticides.

TES is not being conducted by the National Malaria Programme, as there is no malaria transmission in the country. The role of the Maldives Food and Drug Authority (MFDA) is to ensure the quality of WHO-approved diagnostics and imported malaria drugs. RDTs and antimalarial drugs are only available with the national programme. MFDA conducts inspection at the port of entry, and hands over the medicines to the Health Protection Agency (HPA). As per the new AMR Containment Regulation (in the draft stage), it is mandatory for national programs to submit surveillance reports to the national committee. In 2018, the country reported 2 imported *P. vivax* cases from southern India.

In order to remain malaria-free, surveillance is a key intervention; Maldives requires support to train expert microscopists and PCR. Availability of medicines is a major issue and needs to be addressed, given that there is a buffer stock of drugs for *P. falciparum* and
6.3 Sri Lanka (Dr Muzrif Munas, CCP, Anti-Malaria Campaign and Dr Priyani Dharmawardena, Regional Malaria Officer, Ministry of Health)

The last indigenous malaria case in Sri Lanka was reported in October 2012, and the last death in 2007. Sri Lanka was certified malaria-free by WHO in 2016. Since the elimination of malaria, no deaths of imported malaria have been reported to date. Being a tropical country, receptivity and vulnerability are high. Therefore, strategies have been employed to prevent the re-introduction of malaria to the country.

During the past 5 years (2015–October 2019), 218 imported cases of all species were reported, with India and Africa being the major sources. Only one introduced P. vivax malaria case was reported in 2018. Imported malaria presents the challenges of drug resistance and the risk of re-introduction of malaria to Sri Lanka. The highest burden of malaria is reported in the Western Province, where receptivity is very low, and vulnerability is high compared to other provinces.

As per the current National Treatment Guidelines, all diagnosed patients are treated with quality-assured drugs under direct observation, and hospitalized. Each reported case is fully investigated and reviewed by an expert panel.

For mono-infection with uncomplicated P. falciparum, ACT (AL) along with PQ (single dose) is prescribed; for uncomplicated mixed infections with P. falciparum and P. vivax, AL and PQ (for 14 days) is prescribed. For first- and second-line treatment of severe P. falciparum malaria infection, IV artemunate and DHA-PIP are given respectively. In case of mono-infection with P. vivax and P. ovale, CQ and PQ (for 14 days) are given, and for patients infected with other malaria parasites such as P. malariae, CQ and PQ are given. Each case is followed up both clinically and parasitologically until the completion of treatment, and until the parasitaemia registers zero.

A total of 218 malaria cases were imported into Sri Lanka from 2015–2019: India contributed the maximum (80), followed by Uganda (17), Republic of South Sudan (15), Ethiopia (14), Republic of South Africa and Republic of Guinea (9). Malaria cases reported from 2015 to October 2019 have shown the following trend: 155 (71.1%) Sri Lankans and 63 (28.9%) foreigners are affected, whereby 216 (99%) of patients are below 18 years of age.

Among the affected population, 199 (91.3%) are males and only 19 (8.7%) are females. Africa contributes to 119 (54.6%) of malaria cases, followed by 97 from Asia (44.4%) and two from Oceania (0.9%).

In 2015, P. falciparum and P. vivax contributed equally, while in 2018, P. vivax was the major species. Around 151 cases (69.3%) were completely followed-up, 41 (18.8%) were lost to follow-up and in 26 cases (11.9%), the follow-up is continuing.

Among the 218 imported cases, 90 cases were due to P. falciparum, 108 due to P. vivax, 17 due to P. ovale, two due to P. malariae and one P. knowlesi. They were treated according to national guidelines. Out of 22 severe P. falciparum cases, 14 were treated with i.v AS, 10 were followed up for 28 days and two showed late treatment failure (80% efficacy). Eight cases were administered oral ACT seven were fully followed up and one showed LTF (86% efficacy).
Out of 68 non-severe *P. falciparum* cases, 68 were treated with ACT, 61 were fully followed up until day 28, and two showed LTF (96% efficacy). No treatment failure was seen in severe *Pf* cases in 2016–2017. As part of iDES studies from 2015–2019, no *Pf* treatment failure was observed. Similarly, in *P. vivax* and *P. ovale* infections, 100% efficacy of CQ was observed.

Out of 59 *P. vivax* cases treated with primaquine for one year, five relapse cases (8.5%) were observed, whereas none of the 12 *P. ovale* cases treated with Primaquine, showed relapse. Five uncomplicated cases imported from India and Saudi Arabia in 2016–2017, showed relapse on varied days, ranging from Day 40 to Day 414. They were completely cured after repeated treatment.

Dr Munas and Dr Dharmawardena also touched upon the progress made and the challenges faced by Sri Lanka. Hospitalization of all malaria patients, adherence to treatment guidelines and close follow-up are some of the best practices of Sri Lanka. Imported cases are a challenge for the country. Drug procurement and quality of the drugs are other issues.

**Day 2**

7. **Session 4: Updates on quality control and molecular markers**

7.1 **Quality control in TES and iDES: implementation challenges**

(Dr Maria Dorina Bustos)

In areas with very low transmission rates, an adequate number of malaria cases may not be detected at sentinel sites. The surveillance system is strengthened to improve case detection among all sectors (private and public). This is done to ensure that all patients receive the full recommended treatment (including a radical cure), and to confirm a complete cure by following up patients at regular intervals.

In these areas, the strengthened surveillance system can also be used to collect and analyse data on drug efficacy. Thus, efficacy monitoring is shifted from using a sentinel site surveillance study, to relying on data collected via routine surveillance systems.

WHO has provided three quality control monitoring templates for TES: QC checklist pre-study; QC checklist interim (during study implementation) and QC checklist study close-out of study. The QC checklist provides immediate, documented feedback on gaps and challenges to improvement. The purpose of the checklist, which is meant to improve on-site TES implementation, is to identify bottlenecks and fix them.

The QC pre-study and interim visit checklists provide: general study information, study sites and site-specific information (training of site staff, site facilities, study documents, resources, materials, clinical and laboratory supplies, drug inventory); study-specific information (copy of ethics approval, Informed consent/assent forms, patient screening and recruitment forms, case report forms, laboratory and microscopy, and data entry forms); and conclusions/comments/section items.

Common findings during QC monitoring showed some transcription errors from the source document (date, age, parasite counts, temperature, etc.), missing data and errors in CRFs. In the case of treatment failure, no information was recorded on the second-line drug given to the patient. There is no informed assent form for children between the ages of 12 and legal adulthood; in such cases, the guardian grants approval.
On-site slide results by a second microscopist (M2), and laboratory logbooks of M1 and M2 are not available. In some district hospitals and health centres, a second-line drug for rescue treatment was not available.

It was also observed that not all countries use the WHO pre-qualified primaquine (from the manufacturers Remedica and Sanofi) and ACT (DHA-PIP, AL), relying instead on whatever the government can procure.

A drug inventory for the proper storage of drugs was not available. And though the temperature-taking technique and thermometers should always be assessed regularly, staff was not properly trained to record temperature in some areas.

There are many challenges to TES preparation and implementation. Common concerns include protocol development, proper site selection, delays in protocol review and approval by national and WHO ethics committees.

Then, there are administrative delays in releasing funds, leading to missed peak transmission seasons. There is the failure to adhere to study protocols, as also inadequate documentation and reporting systems, missed information, the challenges of supervised treatment (for P. vivax TES, compliance with 14-day PQ therapy); and the quality of slides.

Other challenges include the adherence to study protocol, missed assent from older children, incomplete documentation and reporting systems, and irregular supervisory visits by the PI or medical supervisor (especially at start-up implementation).

Pregnancy test for women and female minors (9–17 years) may be difficult in some cultures, leading to female minors and unmarried women being excluded from the efficacy study. Remote areas are difficult to access in the rainy season, leading to missed follow-up days. Laboratory challenges include poor slide preparation, missed mixed infections, and others.

For genotyping of malaria parasites, Msp1, 2 and GLURP (glutamate-rich protein) need to be done together and not sequentially, in order to differentiate recrudescence from reinfection. Inclusion of pfmdr copy numbers in countries with a history of mefloquine use (Greater Mekong Region) and a material transfer agreement (MTA) between country and reference laboratory, are mandatory.

Due to the high, day 3 positivity rate in the GMS, there is a need to repeat smear and temperature checks for non-febrile cases until negative, and for weekly follow-ups till Days 28/42.

Researchers are validating microscopy by PCR, which leads to difficult interpretation. Though some countries do it as part of their internal QC monitoring protocol, this complicates data analysis and is not a WHO requirement. Comparative trials for surveillance are also not recommended. Additional research questions add extra burden on field staff and compromise the quality of TES implementation.

Other challenges in iDES are proper training in the use of many reporting forms, defined standard operating procedures timely on-line data entry at the field site; regular field supervision, the inclusion of patients from the private sector and data analysis.

7.2 Phenotypic and genotypic monitoring of resistance: GMS experience (Dr Benoit Witkowski, Pasteur Institute, Cambodia)

The emergence and geographic spread of artemisinin-resistant P. falciparum in the Greater Mekong subregion (GMS) represents a serious threat to global malaria control, and to
aspirations to eliminate malaria. Four ACTs have been recommended by WHO in Cambodia: DIP, ASMQ, AS-SP and ASAQ. High treatment failure rates were identified in Cambodia (2010–2017 DP 50%, 2016 ASAQ 20%).

For mefloquine resistance, the molecular marker identified is the Mdr1 gene amplification. Different Kelch13 mutations have been identified as molecular markers for artemisinin partial resistance. Molecular marker for PIP resistance is the Plasmepsin 2–3 (Pfpm 2–3) gene amplification. For amodiaquine, a marker has not yet been established. In Africa, pfmdr1-YYY haplotype is associated with resistance to amodiaquine. However, in Cambodia, whole genome sequencing analysis showed that in vitro amodiaquine resistance is not associated with YYY haplotype, and treatment failures are not associated with pfmdr1-YYY haplotype.

Following the introduction of ASMQ, a decrease in the frequency of the marker of resistance to PPQ has been seen. For now, ASMQ efficacy is very good but this need to be monitored as the marker of MQ resistance has been identified in a case with therapeutic failure (one case).

The triple mutant strains with molecular markers for resistance to MQ & PPQ has been identified. This should be considered in the implementation of treatments with a combination of artemisinin, MQ and PPQ. Past TES with AL and AS-AQ have shown <90% efficacy but molecular markers for resistance to lumefantrine and amodiaquine has not be identified. Therefore, the addition of lumefantrine to amodiaquine due to a supposedly opposed resistance pattern should be carefully addressed. Artesunate-pyronaridine (Pyramax™) displays very good therapeutic efficacy in Cambodia.

Parasite resistance selection is more influenced by the partner drug, than artemisinin itself. Since molecular tools are not always available, there is a need for phenotypic confirmation. For example, emergence of artemisinin resistance is often associated with multiple resistance affecting several partner drugs. Molecular detection of the Kelch 13 mutant should followed by validation, using currently available tools.

7.3 **Role of the Malaria Elimination Research Alliance and ICMR in supporting the TES network in the SEA Region (Dr Manju Rahi, ICMR)**

The Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare supports the national programme in control of malaria through focused research/operational research studies. It identifies cutting edge areas of science, translated for the field, and ultimately into policy. ICMR has a network of 26 institutes/centres across the country, out of which 10 are dedicated to the research of malaria and other vector-borne diseases.

ICMR’s National Institute of Malaria Research (NIMR), is a WHO-recognized malaria RDT lot-testing laboratory. The performance of RDTs has been evaluated in comparison with microscopy and PCR, for malaria diagnosis. They are especially useful for inaccessible/difficult-to-reach areas. The data generated by more than 20 RDTs, helped their introduction and registration in the national programme. Regular monitoring assures the supply of quality RDTs in the public health system. Data on insecticide resistance is also generated periodically and provided to the National Programme.

ICMR-NIMR, Delhi and ICMR-Vector Control Research Centre (VCRC) Puducherry, are recognized as WHO collaborating centres for carrying out Phase I and Phase II testing and evaluation of insecticides, respectively, and are now being accredited as good
laboratory practice (GLP) laboratories. Both centres are equipped to undertake phase II and phase III evaluation of public health products as well.

India has a longstanding tradition in malaria research through many organizations. However, there is very little cross-communication, harmonization and shared-learning amongst research communities. In light of this, ICMR has established the Malaria Elimination Research Alliance (MERA India) with an aim to harness and reinforce research in a coordinated and combined manner and make a tangible impact on malaria elimination. It will provide a common platform to the research community to strengthen the efforts of the national programme in eliminating malaria.

ICMR has been carrying out TES in India through its institutes NIMR and NIRTH. From 2005 to date (2019) and in collaboration with NVBDCP, these institutes have been conducting studies of the efficacy of AS+SP and AL in P. falciparum and CQ in P. vivax malaria across 25 sentinel sites in the states of Odisha, Jharkhand, West Bengal, Assam, Maharashtra, Chhattisgarh, Madhya Pradesh, Karnataka, Gujarat, Tripura, Mizoram, Dadra and Nagar Haveli, Rajasthan, Andhra Pradesh and Arunachal Pradesh. TES have been carried out in more than 6000 patients. CQ has been found effective against P. vivax.

The information generated has led to a ban of the monotherapy of artemisinin for uncomplicated malaria (2009), as well as the phasing-out of CQ in treatment of P. falciparum malaria (2010). It has also led to the introduction of AS-SP for P. falciparum, and the replacement of AS-SP with AL in the north-eastern region (2013).

As India moves towards malaria elimination, the shift from TES to iDES needs to be made over time. To undertake iDES, the routine surveillance system needs to be very robust, and each and every case must be enrolled in iDES. Since, India still has a comparatively large caseload, covering all cases may not be possible. Hence, representative sampling may be undertaken, in consultation with the national programme.

8. Session 5: Harmonization of treatment regimen and evidence to policy (Panel discussion chaired by Dr Kamini Mendis)

While most of the currently-used ACTs are effective in the BBINS countries, points for discussion include the current situation in India, and when to review the treatment regimen and evidence to change policy. The WHO cut-off criteria of 10% treatment failures to AS-SP was observed in north eastern India in 2014, prompting the programme to change to AL as the first-line drug.

Over the years, molecular results from the rest of the country are showing dhps and dhfr double and triple mutations, signs that SP can soon be compromised. Artesunate is masking the efficacy of SP. It’s a matter of time that artesunate efficacy is also compromised, and functional Kelch 13 mutations appear. The national drug committee and programme must agree on the criteria for a drug policy change. One must also take into account the widespread use of AL in the private sector, elsewhere in the country.

9. Session 6: Presentation of country plans and budget: TES + MM and iDES

**Bangladesh**

For 2020, Bangladesh plans TES at two sites in the Chittagong Hill Tracts: in Naikongchiri to test AL+PQ against *P. falciparum* malaria and in Alikadan, to test CQ+PQ14 against
P. vivax malaria. The proposed budget for the two sites is US$ 98 000 and US$ 100 000 respectively.

**Bhutan**

The country proposes to do iDES nationwide, and monitor all cases: imported and indigenous, severe and uncomplicated *P. falciparum* and *P. vivax* malaria. It needs support for additional microscopy training for newly-recruited laboratory technicians, and new doctors and health assistants in case management. The program also plans to modify the NTG, to introduce ASMQ as the second-line drug and to include iDES as part of the drug policy to monitor drug efficacy nationwide. The requested budget for 2020 either from Global Fund or WHO, is US$ 10 000.

**India**

In 2020, the country proposed to conduct TES at eight sites: four *P. falciparum* sites testing ACT, four *P. vivax* sites testing CQ, and four sites for iDES. The proposed *P. falciparum* sites are Bareilly/ Badaun in Uttar Pradesh, Jhabua in Madhya Pradesh, west Singbhumi in Jharkhand and Bastar in Chhattisgarh.

The proposed *P. vivax* sites are Mewat in Haryana, Shivpuri in Madhya Pradesh, Gondia in Maharashtra and North 24 Parganas in West Bengal, at US$ 45 000 per site. Implementers will be NVBDCP+NIMR and/or NVBDCP+NIRTH. In 2021, India proposes to conduct TES at another 12 sites.

For iDES, the four proposed sites in 2020 to follow up all *P. falciparum* and *P. vivax* cases, are the low endemic districts of Himachal Pradesh, Kerala, Rajasthan and Orissa, also with a proposed budget of US$ 45 000 per site. NVBDCP and ICMR will be the implementers.

**Nepal**

The last TES was conducted 2013–2014. Since *P. falciparum* has low prevalence and wide distribution, and *P. vivax* has very focal distribution, the programme proposed TES for *P. vivax* malaria testing CQ+PQ14, and iDES for *P. falciparum* malaria testing AL. There will be 6 sites distributed throughout the country, at US$ 5000 per site.

**Sri Lanka**

The programme will pursue iDES on all reported cases and will include the identification of the source of infection, especially those from drug-resistant areas, for better case management. Proper treatment, hospitalization and close follow-up will be observed as per the country SOPs of the NTGs. Microscopy training is needed for the government and private sector public health laboratory technicians (PHLT) to be conducted annually, and refresher training on case management for all new doctors and practising physicians. The Government of Sri Lanka will provide the funds.
10. Session 7: Conclusions and recommendations

10.1 Conclusions of the Meeting:

➢ Most countries in the region have shown a decline in malaria cases.
➢ First-line ACTs in all countries are currently effective for both \textit{P. falciparum} and \textit{P. vivax} malaria.
➢ \textit{P. falciparum} Kelch-13 mutations (marker for artemisinin partial resistance), have been identified in a few cases in Bangladesh and India. Delayed clearance or ACT failure was not observed in the patients carrying these mutations. Work is ongoing to conduct a TES in the areas where the Kelch 13 mutations were reported.
➢ Considering the challenges for TES, especially due to a decline in the number of cases for enrolment, the enrolment criteria and study areas should be adapted as per need, without compromising technical/ethical issues.
➢ Countries need to prepare TES protocols as per prescribed templates, with realistic budgets for smooth approvals at all levels. Countries and WHO need to explore possible sources of funding, e.g. the Global Fund, where applicable.
➢ The approval process of TES protocols needs to be minimized at every level (country, WHO) to ensure timely initiation.
➢ India should review evidence for a change in treatment policy, with technical support from WHO and NVBDCP, and should organize technical expert group meetings with participation of WHO.
➢ A data-sharing platform should be created specifically for the BBINS network by WHO, in addition to the existing “threat maps” and the website. The countries should also share data/information of imported cases, directly with relevant countries.
➢ For iDES integrated within the programme as part of the surveillance system, ethics committee approval is not mandatory.
➢ Countries should update treatment guidelines regularly, based on TES data and WHO treatment guidelines.

10.2 Recommendations made to the countries of the BBINS Network

➢ Results/reports of TES should be shared with respective country programmes as soon as these are completed, and countries encouraged to publish the same in national/international journals.
➢ Countries should conduct further investigation on reports of Kelch 13 mutations.
➢ Countries should update treatment guidelines regularly, based on TES data and WHO treatment guidelines.
➢ Countries should strengthen capacities for microscopy. QA for microscopy should be ensured for TES. The External Competency Assessment in Malaria Microscopy (ECAMM) should include laboratory technicians engaged in TES studies.
➢ Countries should share data/information of imported cases directly with the relevant nation(s) of origin.
10.3 Recommendations made to WHO

➢ The approval process of protocols at country offices, the Regional Office and HQ should be streamlined to avoid delays.
➢ WHO should support QA for PCR and molecular markers in the network / region.
➢ WHO should consider the periodic inclusion of Myanmar, Thailand and Indonesia at BBINS meetings, and of India and Bangladesh at GMS Network meetings.
Annex 1

Agenda

Day 1: Tuesday, 15 October 2019

Opening session

Chairpersons: Director, National Vector Borne Disease Control Programme (NVBDCP) India and Dr Kamini Mendis, Professor emeritus, University of Colombo, Sri Lanka.

Welcome address and message from Dr Poonam Khetrapal Singh, Regional Director, WHO South-East Asia, read by Dr T.Y. Aditama, Acting Director of the Department of Communicable Diseases (CDS), at the WHO South-East Asia Regional Office.

Objectives, self-introduction by participants and observers, nomination of the Chair and Rapporteur by Dr Neena Valecha, Regional Adviser for Malaria, SEARO.

Session 1: Technical updates

Updates on antimalarial drug resistance, artemisinin resistance, Dr Charlotte Rasmussen, Technical Officer, WHO Global Malaria Programme.

Regional updates and review of TES studies in BBINS, Neena Valecha.

Different drug efficacy surveillance systems: routine TES, integrated drug efficacy surveillance (iDES) in the context of elimination, and importation, Dr Charlotte Rasmussen.

A brief overview on TES protocol template, Dr Maria Dorina Bustos, Technical Officer, WHO SEARO.

Discussion.

Session 2: TES country presentations and discussions

Presentations by TES Principal Investigators of Bangladesh, India and Nepal followed by discussion.

Session 3: Integrated drug efficacy surveillance (iDES) in near-elimination/elimination countries

Presentations by Malaria Programme Officers, Bhutan, Maldives, Sri Lanka, followed by discussion.

Day 2: Wednesday, 16 October 2019

Chairpersons: Dr Md. Nazrul Islam, M&E Expert, National Malaria Elimination and ATD Control Program, CDC Bangladesh and Dr. Benoit Witkowski, Institute Pasteur, Cambodia.

Session 4: Updates on quality control and molecular markers

Quality Control in TES and iDES: implementation challenges, Dr Maria Dorina Bustos.

Updates on Kelch 13, P14 and other molecular markers for resistance, Dr Benoit Witkowski.

Role of Malaria Elimination Research Alliance and ICMR in supporting TES network, Dr Manju Rahi, ICMR.

Session 5: Harmonization of treatment regimen

Harmonization of treatment regimen and evidence to policy: followed by panel discussion, moderated by Dr Kamini Mendis

Professor Emeritus, University of Colombo, Sri Lanka
Session 6: Planning and budget: TES + MM, integrated drug efficacy surveillance

Introduction to group work in country breakout groups; country TES or Drug Resistance Surveillance plans and budgets for 2020–2021, by Dr Maria Dorina Bustos and Dr Risintha Premaratne.

Group work: preparation of presentations.

Session 7: Presentation of country plans

Plenary presentations and discussions on country plans/drug resistance surveillance and budget (15 mins per country); Q&A with Bangladesh, Bhutan, India, Maldives, Nepal, Sri Lanka, by country TES principal investigators/programme managers.

Partners’ comments.

Session 8: Next steps & Conclusion of meeting

Conclusion, next steps and recommendations: Dr Neena Valecha, Dr Charlotte Rasmussen.
Annex 2

List of participants

Government Nominees

**Bangladesh**

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Mr Singay Dukpa  
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**India**

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Dr Kuldeep Singh  
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Sr. Technical Officer – III  
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**Maldives**

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Medicines for Malaria Venture  
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**WHO Secretariat**

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Dr Charlotte Rasmussen  
Technical Officer  
Global Malaria Programme  
Geneva, Switzerland
In the Asia-Pacific region, the monitoring of the efficacy of antimalarial drugs including artemisinins and artemisinin-based combination therapies (ACTs) has become a routine activity of the national malaria programs using a standardized WHO therapeutic efficacy study (TES) protocol. It aims to identify early signs of resistance of recommended treatment regimens to drive evidence-based review and update of a country's national drug policy.

The 4th Meeting of the BBINS Malaria Drug Resistance Monitoring Network (Bangladesh, Bhutan, India, Nepal and Sri Lanka) convened in New Delhi, India on 15–16 October 2019. The discussions highlighted the results of therapeutic efficacy studies including updates on molecular markers for drug resistance, showing that the 1st-line artemisinin-based combinations therapies (ACT) in all countries are currently effective against both P. falciparum and P. vivax malaria; countries to further strengthen malaria microscopy QA; and adopt iDES for monitoring of malaria drug efficacy in areas with low malaria cases as part of the programme’s elimination surveillance activities. Also discussed were workplans for continuing studies over the next two years.
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