

Summary report on the

Eighth intercountry meeting of national malaria programme managers from HANMAT and PIAM-Net countries

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Islamabad, Pakistan
12–14 December 2016



**World Health
Organization**

Regional Office for the Eastern Mediterranean

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1. Introduction

The World Health Organization (WHO) Regional Office for the Eastern Mediterranean in collaboration with the Government of Pakistan convened a meeting of the Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT) and the Pakistan–Islamic Republic of Iran–Afghanistan Malaria Network (PIAM-Net) from 12 to 14 December 2016 in Islamabad, Pakistan.

The objectives of the meeting were to:

- review progress, challenges and problems encountered in the implementation of malaria control and elimination strategies, and provide technical updates including the situation of artemisinin resistance;
- review results of drug efficacy monitoring studies conducted in 2015;
- plan the future activities of HANMAT and PIAM-Net;
- review implementation of planned activities for strengthening border coordination among PIAM-Net countries.

Participants included malaria managers and/or focal points for drug resistance monitoring from six countries in the WHO Eastern Mediterranean Region – namely the Islamic Republic of Iran, Pakistan, Saudi Arabia, Somalia, Sudan and Yemen – as well as Eritrea and Ethiopia from the WHO African Region. Also in attendance were staff from WHO headquarters Global Malaria Programme and the Regional Office for the Eastern Mediterranean, focal points from the WHO African Region and malaria experts. Participants from Afghanistan, Djibouti and South Sudan were not able to participate due to logistics problems.

H.E. Dr Assad Hafeez, Director General, Ministry of National Health Services, Regulations and Coordination, Islamabad, Pakistan inaugurated the meeting. Dr Hafeez emphasized the commitment of the Government of Pakistan to the global targets for malaria control

and elimination, and reiterated support for the work of the networks and on border coordination.

Dr Hoda Atta, Coordinator, Regional Office for the Eastern Mediterranean, highlighted that the meeting aimed to share the latest developments on the trend of disease, and updates on new and existing challenges in countries including antimalarial drug resistance and WHO strategies for its containment, vivax malaria and difficulties faced in its elimination, as well as HRP2 deletion (already confirmed in Eritrea) and its possible consequences on the targets for malaria eradication. Dr Atta reminded participants that, in September 2016, the Global Fund pledged nearly US\$ 13 billion for the next 3 years for continuation and scaling up of interventions toward elimination of AIDS, tuberculosis and malaria. A more coordinated approach was required to access allocated resources, as well as a plan for their more efficient use to provide quality services and interventions in the coming years. Dr Atta noted that World Malaria Day 2017 would be an opportunity for advocacy, awareness raising and securing commitments required.

2. Summary of discussions

The meeting discussed monitoring drug efficacy, artemisinin resistance and the plan for its containment. The in vivo study results are the gold standard for monitoring drug efficacy and guiding national treatment policies. Molecular markers, in vitro studies and pharmacokinetics studies can be supportive to the in-vivo outcome to confirm resistance. Treatment failure in a patient is not always due to drug resistance, but can also be due to other factors including inadequate drug concentration (resulting from inadequate dosage, poor quality drugs, compliance issues, pharmacokinetic factors, drug interactions, etc.) and patient immunity.

WHO has developed a template protocol for monitoring therapeutic efficacy of malaria drugs. The key elements in the protocol are (i) patients are followed up for 28 or 42 days; (ii) clinical and parasitological cures are assessed; (iii) polymerase chain reaction (PCR) analyses are done on samples from patients with treatment failure to distinguish between recrudescence or re-infection; (iv) it can be performed in all malaria transmission settings; and (v) day 3 positivity rate is calculated as parasitological marker for partial artemisinin tolerance. The WHO template protocol can be used both for studies of *P. falciparum* and *P. vivax*. WHO recommends that malaria-endemic countries monitor therapeutic efficacy of first- and second-line antimalarial medicines using the WHO-recommended dose regimens.

The WHO Research Ethics Review Committee determined that all female patients of childbearing age should be tested for pregnancy prior to enrolment in therapeutic efficacy studies and should use contraception during the study period. If it is culturally inappropriate that unmarried women and female minors of childbearing age (9–17 years) are tested for pregnancy, they should be excluded from the study. Quality control and data validation are critical to obtain reliable data that can guide national level treatment policy. WHO has developed software for data management that is available to countries. The software enables investigators to double enter the data (with a checking system) and analyse data as per protocol and Kaplan-Meier analysis.

An update was provided on the current situation of artemisinin resistance. Emergence and spread of artemisinin resistance in the Greater Mekong subregion presents a major threat to global malaria control and elimination efforts. Artemisinin resistance is defined as delayed parasite clearance following treatment with an artesunate monotherapy or with an artemisinin-based combination therapy (ACT); this represents partial resistance. A molecular marker of

artemisinin resistance was recently identified. Mutations in the Kelch 13 (K13)-propeller region were shown to be associated with delayed parasite clearance both in vitro and in vivo. The identification of the K13 marker for artemisinin resistance has allowed for a more refined definition of resistance that includes information on the genotype. However, as the list of mutations associated with artemisinin resistance is still evolving, so the definition of artemisinin resistance will continue to evolve. There are more than 200 non-synonymous mutations in the K13 gene.

Suspected artemisinin resistance is defined as:

- $\geq 5\%$ of patients carrying K13 resistance-confirmed mutations; or
- $\geq 10\%$ of patients with persistent parasitaemia by microscopy at 72 hours (± 2 hours; i.e., day 3) after treatment with ACT or artesunate monotherapy; or
- $\geq 10\%$ of patients with a half-life of the parasite clearance slope ≥ 5 hours after treatment with ACT or artesunate monotherapy.

Confirmed endemic artemisinin resistance is defined as:

- $\geq 5\%$ of patients carrying K13 resistance-confirmed mutations, all of whom have been found, after treatment with ACT or artesunate monotherapy, to have either persistent parasitaemia by microscopy on day 3, or a half-life of the parasite clearance slope ≥ 5 hours.

Patients with a delayed parasite clearance response are still cured by ACTs provided that the partner drug remains effective, even in areas of high prevalence of K13 mutation (China, Myanmar and Viet Nam). However, this is not the case in Cambodia and Thailand, where there is concomitant resistance to partner drugs such as mefloquine and piperaquine.

There have been some reports of delayed parasite clearance during routine therapeutic efficacy studies of ACTs conducted in Africa; however, these reports have not been consistent over time. K13 mutations, including C580Y, have also been reported from many African countries. However, these mutations have not been associated with slow parasite clearance. A578S is the most frequent allele observed in Africa, but it is not associated with clinical or in vitro resistance to artemisinin. In South America, there have been reports on delayed parasite clearance from Suriname and Guyana. However, confirmatory studies did not confirm high day 3 positivity and K13 mutations. Studies on K13 mutations are underway in Guyana. In studies conducted in countries in the Eastern Mediterranean Region, in collaboration with NAMRU-3, no mutations were detected in the single nucleotide polymorphisms at 20 locations on K13 genes.

In addition to artemisinin resistance, high treatment failure rates with dihydroartemisinin-piperaquine (DHA-PQ) have been reported from Cambodia after the combination was introduced in 2008 as first-line treatment. The high treatment failure rates observed with DHA-PQ are associated with piperaquine resistance, which has been present in Cambodia since 2002 and has spread geographically from western to north-eastern Cambodia. High treatment failure rates (>10%) with DHA-PQ have also been reported from Viet Nam.

It was emphasized that drug resistance monitoring plays a critical role in the global fight against artemisinin resistance. Routine monitoring must continue to ensure that the recommended ACTs are effective, that changes in national treatment policies are implemented in a timely manner, and that artemisinin resistance is detected early.

Assessment of K-13 propeller-region mutants will greatly facilitate the tracking of artemisinin resistance as it emerges. In addition, DHA-PQ

molecular markers for piperazine resistance should be monitored in countries in the Eastern Mediterranean Region where DHA-PQ is available in either public or private facilities.

Technical updates were provided on the presence of HRP2 deletion in Eritrea, and its possible consequences for malaria confirmation by HRP2-based rapid diagnostic tests. Neighbouring countries – Ethiopia, Somalia and Sudan – were advised on the importance of introducing appropriate surveillance modalities for HRP2 deletion and on available options in case of detection.

Plasmodium vivax is the main species of malaria in Afghanistan and Pakistan, and is starting to increase in other countries where *P. falciparum* malaria is decreasing. There is a misconception that *P. vivax* malaria is a mild disease and does not result in death. It was highlighted, however, that severe malaria resulting from infection with *P. vivax* is increasingly reported in Pakistan. Furthermore, the high prevalence of G6PD deficiency in some areas of the Eastern Mediterranean Region is a challenge, with primaquine the only available medicine for elimination of hypnozoites and prevention of relapse.

Participants reviewed the epidemiology of *P. vivax* malaria, its proper case management (including safe use of primaquine), use of point-of-care G6PD tests, and strategies for when testing is unavailable and radical therapy not possible. It was clear that a gap exists in knowledge and proper practice of management of vivax malaria that needs to be addressed.

An update was shared on the funding cycle for 2017–2019, and how to prepare funding requests. Participants reviewed the four new strategic directions of the Global Fund, and identified countries' expectations from WHO relating to objectives and the cycle of grants including: the Country

Coordinating Mechanism, country dialogue, concept note, grant preparation, application, implementation and monitoring and evaluation.

3. Recommendations

To Member States

1. For the prevention of drug resistance, and in keeping with good clinical practice, intensify efforts to scale up testing of suspected malaria cases before treatment with an antimalarial. Presumptive treatment of malaria should be phased out as soon as possible:
 - establish an updated roster of qualified microscopists to participate in external competence assessment to be organized by WHO;
 - in Djibouti, Pakistan and Sudan, enforce regulations to ban the use of injectable antimalarials for the treatment of uncomplicated malaria;
 - expedite development and finalization of protocols for monitoring in vivo efficacy of first-line and second-line drugs and other potential medicines for treatment of both falciparum and vivax malaria, to be submitted to ethical committees at least 6 months before start of transmission season, and put in place quality control and data validation system as a mandatory step;
 - allocate enough resources in the next submission of grant requests to the Global Fund for therapeutic efficacy studies, operational research on vivax malaria surveillance/treatment and G6PD deficiency epidemiology, and risk mapping.
2. Noting the detection of HRP2 deletion in Eritrea, neighbouring countries should establish appropriate surveillance activities such as baseline surveys and sentinel site surveillance, using existing infrastructure where possible, including therapeutic efficacy study sites.

3. Continue to provide needed data for finalization of regional risk mapping at district level for all endemic countries, as a baseline and monitoring tool for regional action plan; conduct in-depth assessment of malaria surveillance and information systems in priority countries (Pakistan and Sudan).
4. Implement WHO recommendations for radical treatment of vivax malaria through expansion of safe use of primaquine, including use of point-of-care of G6PD deficiency tests wherever possible and clinical follow up where not possible, and pharmacovigilance of the therapy.

To WHO

5. Continue to support HANMAT and PIAM-Net activities:
 - in consultation with countries, develop the mandate, scope of work, objectives, new terms of reference and operational plan for the networks for endorsement at the next meeting.
 - conduct joint training on quality control of therapeutic efficacy studies for countries of the Eastern Mediterranean and African regions;
 - develop a follow-up system for each country to ensure protocols for therapeutic efficacy studies are submitted on time, and establish a regional roster for certified malaria microscopists for expansion of quality assurance activities in the networks and to improve quality of therapeutic efficacy studies.
6. Provide technical and logistics support for surveillance activities related to the detection of HRP2 deletion in countries neighbouring Eritrea.
7. Organize a training-of-trainers workshop for radical treatment of vivax malaria, including use of point-of-care G6PD deficiency tests.
8. Organize regional World Malaria Day 2017, in coordination with the Ministry of Health of Saudi Arabia, in Jeddah.



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