Summary report on the

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

WHO-EM/MAL/384/E

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 of Health, 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:

- ≥5% of patients carrying K13 resistance-confirmed mutations; or
- ≥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
- ≥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:

- ≥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.