Summary report on the
Seventh intercountry meeting of national malaria programme managers from HANMAT and PIAM-net countries

Amman, Jordan
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1. Introduction

The WHO Regional Office for the Eastern Mediterranean in collaboration with the Government of Jordan convened a meeting of the national malaria programme managers of countries in the Horn of Africa Network for Monitoring Antimalarial treatment (HANMAT) and the Pakistan, Islamic Republic of Iran and Afghanistan Malaria Network (PIAM-Net) from 25 to 26 November 2015. The objectives of the meeting were:

- to enable members from malaria endemic countries of the networks to share their results of studies on monitoring antimalarial drug efficacy;
- to update the regional database with surveillance data on antimalarial drug efficacy; and
- to plan country activities for monitoring drug efficacy and for updating national drug policies in 2016.

In attendance were malaria managers and/or focal points for drug resistance monitoring in 8 countries of the WHO Eastern Mediterranean Region: Afghanistan, Djibouti, Islamic Republic of Iran, Pakistan, Saudi Arabia, Somalia, Sudan and Yemen. Ethiopia, Eritrea and South Sudan from the WHO African Region were represented by the focal point from the WHO Regional Office for Africa.

Dr Hoda Atta, Acting Director of Communicable Diseases and Regional Adviser, Malaria Control and Elimination, inaugurated the meeting. She noted that while the role of the networks had been mainly coordinating surveillance of drug resistance, the meetings and training courses of the networks sometimes included other topics such as pharmacovigilance and the use of serological techniques. She asked participants to review the objectives of the networks and address all issues related to case management and drug resistance in line with the Global Technical Strategy.
2. Summary of discussions

The meeting discussed artemisinin resistance and monitoring efficacy and the plan for its containment. The emergence of artemisinin resistance in four countries in the Mekong subregion presents a major threat to global malaria control and elimination efforts. Artemisinin resistance is defined as delayed parasite clearance (day 3 positivity rate); this represents a partial resistance not necessarily associated with treatment failures of artemisinin-based combination therapy (ACT) or artesunate monotherapy. If day 3 positivity increases to $\geq 10\%$, artemisinin resistance is suspected, and must be subsequently confirmed with a study of artesunate monotherapy over 7 days. Most patients who have delayed parasite clearance following treatment with ACT clear their infections. However, this is not the case in Cambodia and Thailand, where there is concomitant resistance to the partner drugs such as mefloquine and piperaquine.

A molecular marker of artemisinin resistance was recently identified. Mutations in the Kelch 13 (K13) propeller region are 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 have been some reports of delayed parasite clearance during routine therapeutic efficacy studies of ACT conducted in Africa, but these reports have not been consistent over time. K13 mutations have also been reported from many African countries. However, these mutations have not been associated with slow parasite clearance. In South America, there have been reports on delayed parasite clearance from Surinam and Guyana. However confirmatory studies did not confirm high day 3 positivity and K13 mutations.
Drug resistance monitoring plays a critical role in the global fight against artemisinin resistance. Monitoring must continue to ensure that the recommended ACTs are effective, that changes in national treatment policies can be implemented in a timely manner, and that artemisinin resistance can be detected early. Assessment of K13 propeller region mutants will greatly facilitate the tracking of artemisinin resistance as it emerges.

Focal persons of malaria endemic countries shared their updates on the latest results of therapeutic efficacy studies and treatment policies. Countries implementing elimination strategies such as Saudi Arabia have few cases, making it difficult to conduct drug efficacy studies. In Saudi Arabia there was a workshop on updating the national policy of malaria treatment in November 2015; the policy document is under review and will be available soon. In the Islamic Republic of Iran treatment and diagnosis are free of charge for all: antimalarial drugs are only available in the public health facilities. Monitoring drug efficacy of falciparum cases is routine practice for all cases on day 3, 7, 14, 28 since 2012. The latest results of monitoring of antimalarial drugs showed 100% adequate clinical and parasitological response (ACPR) for the first-line antimalarial for both falciparum and vivax.

In collaboration with WHO a new study on therapeutic efficacy of chloroquine in vivax cases has started, noting that majority of cases in the Islamic Republic of Iran are vivax.

In Afghanistan the results of a therapeutic efficacy study shows that artemether–lumefantrine has 100% ACPR on day 28 in both falciparum and vivax arms. Treatment was faster in vivax patients compared to falciparum (at day 1, 75% versus 63%, P<0.05, at day 2, 97% versus 96% (p>0.2). There are different drugs available in the market with no authorization for controlling the importation of the drug in the public and private sectors mainly due to a weak drug regulatory system.
Activities implemented in Djibouti on malaria case management include training on diagnosis, quantification of ACTs, rapid diagnostic tests and laboratory products. Challenges faced by the programme have been monitoring antimalarial efficacy and quality assessment of malaria diagnosis.

In Pakistan, studies were conducted in Balochistan/Zhob and Federally Administered Tribal Agencies/Kurram Agency in 2015. The results achieved so far on the efficacy of dihydroartemisinin–piperaquine are encouraging. There has been a ban on the introduction and use of oral monotherapies in 2008 but conditional permission to produce injectable artemether has been given and sold to hospitals and for pre-referral cases. As there are 300 manufacturing companies the Ministry of Health is making strenuous efforts to impose a complete ban on this drug. Challenges facing the malaria control programme for proper management of malaria cases in Pakistan include availability of medicines that are not in the national drug policy in the market, use of injectable medicines for uncomplicated malaria and incomplete treatment of very large numbers of malaria cases without confirmation since many doctors do not rely on rapid diagnostic tests or microscopy results.

In Sudan, currently artemether–lumefantrine (AL) is the interim first-line treatment of uncomplicated malaria. With availability of the results of the therapeutic efficacy studies on artesunate and sulfadoxine–pyrimethamine (AS+SP) in Gedarif/Algeneina and Gedarif/October with ACPR of 81.8% and 89.5%, respectively, there is a consensus that this is time to update national treatment policy. The challenges are to decide on alternatives for first line and manufacturers’ prequalification, noting that the prolonged process in the new setting of the Ministry of Health delayed the site opening this year, in addition to the risk of expiration of dihydroartemisinin–piperaquine before the end of the study. More efforts need to be made on the rational use of drugs. Previous malaria programme review in Sudan raised concerns on the use of artemether
injection for uncomplicated malaria (monotherapy): very little has been done to prevent this and the drug is still available in the market, despite efforts made for training and advocacy. The most effective way for the country to stop the irrational use of this drug is through a ban imposed by the government and insurance of its removal from the market. The drug regulatory system should be activated to prevent over-the-counter drugs without prescription.

The malaria programme in Yemen published an article in 2015 on the high efficacy of two artemisinin-based combinations: AS+SP and AL for treatment of falciparum in Yemen based on studies conducted up to 2013. The studies concluded that AS+SP remain the effective drug for uncomplicated falciparum malaria in Yemen. AL is also highly effective and can be considered as an alternative to AS+SP for the treatment of falciparum malaria. Challenges for future conduct of efficacy studies include lack of trained clinical staff, national core group of experts, infrastructure, human resources and insufficient budget. The programme has updated their national malaria treatment policy according to the new WHO recommendation. The updated policy that needs to be endorsed added primaquine to be used to clear falciparum gametocytes.

The results of drug efficacy studies in Somalia show that revision of the national treatment policy is urgently needed. In 2011 the ACPR for AS+SP was reported to be 77.8 % in Jamame, 99% in Jowhar and 95.6% in Jannale. In 2013 the ACPR for AL was reported to be 99% in Jowhar and 100% in Jannale. In 2015 the ACPR for AS+SP in Bosaso was reported to be 87.7%, while for AL in was 97.6%. Malaria programmes encountered some challenges including insecurity in the south–central zone, budget constraints, and implementation of AL twice a day for three days.
In Eritrea, the conclusion of the 2012 studies was that the combination of artesunate and amodiaquine (AS+AQ) remain efficacious in general for the treatment of uncomplicated *P. falciparum* malaria. In South Sudan, based on studies conducted in 2004, the policy was changed in 2005 to AS+AQ as the first-line treatment for uncomplicated malaria. AL was chosen as the second-line regimen and the conducted 2013 study has been put on hold and was not analysed. Sentinel sites for drug resistance monitoring play an important role in monitoring trends. Efforts need to be made to establish a multidrug resistance testing centre and become the basis for establishing a network to monitor local and regional trends.

The meeting discussed progress with sero-surveillance for malaria and its potential use for elimination in the Region. In low transmission settings, additional measures are required to improve sensitivity of surveillance. For malaria, conventional entomological and parasitological measures can lack precision (i.e. require intense sampling). Serological analysis is an additional complementary measure which estimates exposure to infection and in different age groups and integrates exposure over time. Serological analysis of malaria indicator survey samples can be used to identify areas with highest exposure potential to target control and also can be used as an evidence of changes in or absence of transmission. Malaria serology shows good agreement with other measures of infection. Serology assays can be relatively quick and inexpensive. However still there are some challenges including lack of standardized assay and issues with false positives. There is a good amount of experience in some countries in the Region, namely Djibouti, Egypt, Islamic Republic of Iran, Pakistan, Somalia, Sudan and Yemen, which are in different stages of malaria control and elimination, that may be helpful for using serological surveys in programme planning and decision-making towards malaria elimination.

The meeting discussed the lessons of one decade of therapeutic efficacy studies (TES) and the way forward for improving quality. Treatment
failure is not always due to drug resistance. It can be caused by many other factors, including inadequate dosage, poor drug quality, pharmacokinetic factors, patient immunity and compliance. Furthermore, polymerase chain reaction (PCR) analysis must be conducted on treatment failures to determine whether treatment failure during follow-up was due to a true recrudescence (the same parasite) or a re-infection (caused by a new parasite). There are several tools available for monitoring drug efficacy and resistance, including the in vivo study using the WHO protocol (2009), pharmacokinetic studies, in vitro studies, and studies of molecular markers. However, the in vivo study results are the gold standard which is used to determine whether a change in treatment policy is required. Molecular markers and pharmacokinetics studies can be supportive to the in-vivo outcome to confirm resistance.

The WHO template protocol can be used both for studies of *P. falciparum* and *P. vivax*. Study follow-up is recommended over 28 days, but can be extended to 42 days for medicines like dihydroartemisinin+piperaquine. The template protocol has been pre-approved by WHO. The ethical committee determined that all female patients of childbearing potential should be tested for pregnancy prior to enrolment in TES and should use contraceptives during the study. It is not culturally appropriate that unmarried women and female minors of childbearing potential (9–17 years) are tested for pregnancy, implying that they will be excluded from the study. The 2009 protocol can be adapted to the different malaria transmission levels.

Therapeutic efficacy monitoring is defined as the act of overseeing the progress of the study, and of ensuring that it is conducted, recorded and reported in accordance with the approved study protocol. The purpose of monitoring is to verify that: 1) the rights and well-being of the patients are protected; 2) the reported TES data are accurate, complete and verifiable from source documents; and 3) the conduct of the study is in compliance with the currently approved protocol/amendment(s). The
monitoring can be conducted by a locally identified clinician or externally identified qualified person. The frequency of monitoring visits will depend on complexity of the protocol/study, e.g. target number of patients, number of drugs being studied, experience of investigator and study staff and site team’s previous performance.

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. Each country is encouraged to develop its own operational plan, using experiences from other initiatives and programmes, with appropriate targets and timelines, and locally tailored intervention. Resources should be secured from national or donor resources.

2. Urgently review and update the antimalarial drug policy taking into consideration the following:
   - inclusion of single dose of primaquine as a gametocytocidal drug (for *P. falciparum*) (Somalia and Sudan);
   - Inclusion of injectable artesunate as first option for treatment of severe malaria (Somalia, Sudan and Yemen);
   - inclusion of radical treatment of *P. vivax* and *P. ovale* with primaquine (14-day or 8-week regimen) and indication of the treatment of mixed infections according to WHO guidelines (Somalia).

3. In Djibouti, Pakistan and Sudan, take strong action and enforce regulations to ban the use of injectable antimalarials for the treatment of uncomplicated malaria.

4. Continue activities for monitoring in vivo efficacy of first-line and second-line drugs and other potential medicines for treating of both
falciparum and vivax malaria, and collect filter papers for day 0 (preferably two papers) to perform molecular marker analysis of mutations associated with SP resistance as well as K13 mutations for artemisinin resistance.

To WHO

5. In consultation with countries, develop the mandate, scope of the work, objectives, new terms of reference and operational plan for the networks, for endorsement in the next meeting of the networks.

6. Support countries in sharing the results of the drug efficacy studies in international journals, through assistance in developing manuscripts and publication. Collaboration with research institutes is also encouraged.


8. Explore the possibility of expanding the area of work of the networks to include insecticide resistance monitoring.

9. In Somalia, together with the national malaria control programme, organize a meeting with all stakeholders for urgent review and update of the drug policy. This is in response to the 2011 and 2015 studies that found high failure rates with AS+SP in Jamame and Bosaso and a high proportion of SP quintuple mutations in Jowhar and Jamame. The drug policy should consider the efficacy of AL observed during the 2013 study in Jowhar, Janale and Bosaso. The meeting should also review the policy of intermittent preventive treatment in pregnancy and its current value in Somalia, given the decrease in the prevalence observed during the malaria indicator survey in 2013.

10. In Sudan and Pakistan, follow up on action taken for preventing the use of injectable antimalarials for treatment of uncomplicated malaria.