WHO-EM/MAL/372/E

Report on the

Intercountry meeting of national malaria programme managers from HANMAT and PIAM-net countries

Sharm El Sheikh, Egypt
21–22 February 2013

World Health Organization
Regional Office for the Eastern Mediterranean

WHO-EM/MAL/372/E

Report on the

Intercountry meeting of national malaria programme managers from HANMAT and PIAM-net countries

Sharm El Sheikh, Egypt
21–22 February 2013

World Health Organization
Regional Office for the Eastern Mediterranean

Document WHO-EM/MAL372/E/04.13/53

CONTENTS

1. INTRODUCTION

The third intercountry meeting of national malaria programme managers from HANMAT and PIAM-NET countries was organized by the World Health Organization Regional Office for the Eastern Mediterranean in Sharm El Sheikh, Egypt, from 21 to 22 February 2013. The objectives of the meeting were to:

- update the participants about the monitoring efficacy of antimalarial medicines and status of artemisinin resistance.
- present new therapeutic efficacy data from sentinel sites.
- plan for the next round of therapeutic efficacy studies (TES).

National malaria programme managers and focal points for case management attended from: Afghanistan, Djibouti, Islamic Republic of Iran, Pakistan, Saudi Arabia, Somalia, South Sudan, Sudan, Yemen, Ethiopia and Eritrea. WHO staff from headquarters and field staff from Afghanistan, Djibouti, Islamic Republic of Iran, Pakistan, Somalia, Sudan and Yemen also attended the meeting.

The Chair was shared on a rotating basis. The programme and list of participants are included as Annex 1 and 2, respectively.

2. TECHNICAL PRESENTATIONS

2.1 Therapeutic efficacy monitoring and the WHO protocol

M. Warsame /HQ

Treatment failure is not always due to drug resistance, it can be caused by many other factors, including: inadequate dosage, drugs of poor quality, pharmacokinetic factors, patient immunity and compliance. Further, 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.

The methods for conducting a TES were reviewed in detail. The WHO template protocol is designed for studies of *P. falciparum;* however, it can be adapted for studies of *P. vivax.* Study follow-up is recommended over 28 days, but study follow-up can extend to 63 days for medicines which have longer half-lives. The protocol has been pre-approved by the WHO Ethical Review Committee. The ethical committee determined that it would be unethical to include women of childbearing age for whom pregnancy status is unknown, given the unknown safety profile of administration of artemisinin during pregnancy.

The 2009 protocol addresses the changing epidemiology of malaria and the challenges of adequate patient recruitment in low transmission areas, by expanding the baseline parasitemia range. Specifically, in low transmission areas, the lower limit of baseline parasitemia can be reduced to 500 parasites/uL. In very low transmission areas, the baseline parasitemia was reduced to 250 parasites/ul. However, such a low threshold demands highly skilled microscopists. Sample size can also be increased by increasing the age band. For example, patients of up to 10 years could be included in moderate transmission areas, and patients of all ages could be recruited in low transmission areas.

WHO Global Malaria Programme, in coordination with WHO Regional Office, is available to review the TES protocol, facilitate training and monitoring at study sites, provide financial and technical support, provide medicines and filter papers, and assist with quality control, report writing and publications. All countries are encouraged to publish their findings, in order to contribute to the scientific literature of therapeutic efficacy, and ultimately contribute to the creation of evidence and subsequent policy-setting. Journal fees exist for some journals, however articles can be submitted free of charge to the WHO Bulletin and the Eastern Mediterranean Health Journal.

2.2 Update on artemisinin resistance

Dr M. Warsame, WHO headquarters

The emergence of artemisinin resistance in four countries in the Mekong subregion presents a major threat to global malaria control and elimination efforts. Drug resistance monitoring plays a critical role in the global fight against artemisinin resistance. As researchers have yet to identify a molecular marker, currently the best available indicator for artemisinin resistance is the increase in day 3 parasite rate. If this proportion increases to more than 10%, artemisinin resistance is suspected, and must be subsequently confirmed with a study of artesunate monotherapy over 7 days.

An algorithm to help interpret results of TES findings has been developed. An increase in the day 3 positivity rate is indicative of reduced sensitivity to the artemisinin component, while an increase in treatment failure ($\geq$10%) afterwards up to day 28 is indicative of reduced sensitivity to the partner drug. Due to the different mechanisms of action in each drug in the combination, “ACT resistance” is inaccurate and should be avoided. Testing the partner drug alone would be unethical, as it would mean treating a patient with monotherapy. Testing the ACT as recommended, using a TES is the most effective way to determine the efficacy of the partner drug. Countries should have second- and third-line treatments ready, in case a change in treatment policy is needed. If the partner drug is failing, a new ACT could be selected. However, if artemisinin resistance emerges, it will be more problematic to find an alternative.

Maps showing the rates of treatment failure and day 3 positivity for study sites have recently been created. The maps can be customized by treatment, outcome indicator, geographic site, and year. The maps are dynamic, and allow the user to see changes in the study results over time, and to compare selected sites. Following selection, data from can be exported to Excel. Maps will also be available on the web site in the coming months.

2.3 Microscopy for TES

Professor A. Adeel, WHO Temporary Adviser, King Saud University

Microscopy is one of the most important elements for conducting a high quality TES. For the purposes of screening and enrolment, three blood slides are needed per patient, two thick and one thin. Blood slides are used for initial screening (first thick smear), to calculate parasite density and test for mixed infections (second thick smear), and to confirm mixed infection if the thick smear was inconclusive (thin smear). Blood slides are taken throughout the study, on days 2, 3, 7, 14, 21, 28, and subsequently every seven days until study completion. Special rules apply for dealing with low and high parasitic counts. To ensure quality assurance, two qualified microscopists should read the slides independently, and parasite densities should be calculated as an average of the two counts. Discordant results are to be examined by a third, independent microscopist. An excellent reference CD for malaria microscopy is available from the CDC, with examples of over 300 slides. Participants were advised to adhere to the guidelines for microscopy in the TES protocol.

2.4 TES challenges and implementation shortcomings

Dr M. Warsame, WHO headquarters

The following TES challenges were identified by programme managers:

- Poor security in areas of conflict
- Scarcity of good microscopists
- Recruitment of patients in areas of low transmission
  - It has been suggested that studies could be conducted in sentinel sites over a full year, rather than only during the transmission season. This would require a protocol specific to this approach.
  - If caseload is still too low, results could be pooled across sites. However, it is still useful to keep the same sentinel sites, in order to track changes over time.
- Follow-up
  - Selecting incentives for maintaining follow-up must be considered carefully. Study investigators should strive for a balance between giving incentives and coercion.
- Staffing
  - Staff should be hired to work specifically on the TES: health facility staff should not be expected to be responsible for the TES in addition to their regular workload. Staff costs must be part of the TES budget.

Common errors observed during clinical monitoring of TES have included:

- inadequate preparation time resulting in missing the malaria transmission season
- failure to adhere to the study protocol
- failure to recruit patients who live in close proximity to the hospital
- technical problems with parasitological assessment
- quality control and validation
- data entry problems.

The Excel spread sheet used for data collection could be improved to make it more user-friendly, particularly for staff working at the peripheral level. In addition, the Excel sheet could be expanded to include molecular marker data and side-effects. Data from the sentinel sites be incorporated into the national surveillance system with standardized functions for data collection, analysis and exporting.

2.5 Technical monitoring

N. Abdulrab, Ministry of Public Health and Population of Yemen

Variations in study methods and completeness of case report forms have been observed in all sites. A one-page case report form will be developed to enhance feasibility and ease of data collection. External monitoring is not routinely conducted in all countries, but it should be considered an essential aspect of conducting a TES, as it improves the quality of the study and the data, and ultimately protects the researchers.

2.6 Genotyping to differentiate recrudescence from re-infection: methods, techniques and interpretation of data

Dr Hanan El Mohammady Ismail, NAMRU 3

Multiplex PCR allows for detection of multiple genes in the same primer. Three genetic markers include *msp1, msp2* and *glurp*. The nested PCR increases specificity of the PCR. Recrudescence is identified when there is at least one allele in common between day 0 and the day of failure. A new infection is indicated when all alleles are different. PCR can be used for the detection of antimalarial drug resistance genes: for example the detection of mutations in *dhfr* and *dhps* genes.

Over the last year NAMRU-3 has provided analysis of filter papers from Pakistan, Somalia and Sudan. Parasites observed on day 3 will definitely be caused by the same parasite, and therefore PCR analysis is not required. In Somalia, quadruple and quintuple mutations were detected. In Sudan, with the exception of Gadaref, analysis showed that most of the treatment failures were due to reinfections. In Gadaref, 9 of the 13 treatment failures were confirmed recrudescence. Programmes are encouraged to avoid delays in PCR correction of samples, as delays consequently postpone the interpretation of study findings, prompt changes to treatment policy, and extend the time at which patients are at risk of receiving ineffective treatment.