

ASSIGNMENT REPORT ON

**DEVELOPING A SYSTEM FOR MONITORING SUSCEPTIBILITY OF
FALCIPARUM MALARIA TO DRUGS IN PAKISTAN
(1-14 August,1998)**

BY

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1: EXECUTIVE SUMMARY

Drug resistant falciparum malaria is present in Pakistan, both in local inhabitants and among Afghan refugees. Earlier studies of the problem were conducted in a haphazard, non-systematic way. Currently there is no system for continuous monitoring malaria drug resistance in Pakistan. A protocol has recently been developed by WHO for monitoring therapeutic efficacy of antimalarial drugs against falciparum malaria in area of low transmission (WHO /TDR draft 28.2.1997).

Dr Ahmed Awad Adeel visited Pakistan during the period 4-13 August as WHO short-term consultant, to develop a plan for monitoring susceptibility status of malaria parasites in Pakistan to drugs and to conduct a workshop and develop a training program on the subject. During this period the consultant met and discussed with WR Pakistan and with senior national staff. Due to availability of appropriate numbers of malaria cases in Balochistan Province at the time of the study, most of the activities of this consultancy were based in that province. In collaboration with Balochistan Health Directorate, field application of the new test (WHO /TDR draft 28.2.1997) for monitoring drug resistance was initiated in three posts in three health care facilities in the District of Quetta (Balochistan Province). A national workshop was held during the period 11-13 August in Quetta. The participants represented all provinces: Sindh, Punjab, NWFP, Balochistan and Azad Jammu Kashmir as well staff from NIH Islamabad, and WHO Pakistan. Participants in the workshop had the chance to see the monitoring activities being carried out. The workshop discussed and approved a standard protocol for carrying out the test in Pakistan as well as a Plan of Action for implementation of monitoring activities at national level.

2: OVERVIEW

Over the past two decades several surveys were conducted in Pakistan to assess susceptibility of *Plasmodium falciparum* to antimalarial drugs, mainly chloroquine. These were mainly *in vivo* studies based on the extended WHO test (WHO 1973). Results of these tests are shown in ANNEX I. Most of the tests were done in Punjab Province, involving small numbers of cases in each survey. Variable percentages of RI and RII were detected but no cases of RIII were reported. Recently a resurgence of falciparum malaria and spread of resistant strains have been reported. However, information regarding drug resistant malaria in Pakistan remains insufficient due to difficulty of field application of the new *in vivo* test and lack of a system for collection and analysis of such information. In the past few years, WHO working groups been engaged in the development of a protocol for *in vivo* assessment of therapeutic efficacy of antimalarial drugs. A protocol was developed for areas of intense transmission (WHO/MAL/96.1077). This was followed by another draft protocol for areas low transmission/unstable malaria (WHO /TDR draft 28.2.1997). The latter is more suitable for application in Pakistan. These protocols are simpler than the classical WHO standard *in vivo* tests and suitable for application at the peripheral level. In the course of this consultancy the draft protocol for areas of low/unstable malaria was applied in three posts in Pakistan. A workshop was held

while this work was in progress to allow workshop participants to have a practical experience in this procedure. The workshop discussed the protocol in light of this experience and proposed certain modifications to adapt it to local conditions. A Plan of Action and the outline of a program of training on the subject were also discussed and approved in this workshop.

3: FINDINGS:

1: PLANNING AND IMPLEMENTATION OF FIELD WORK:

Plans for this consultancy were reviewed on reporting to WRO Pakistan in 4 August. A meeting held by WR Dr Mohamed Ali Barzgar, attended by Dr Tariq Zulqarnain, epidemiologist Federal Ministry of Health and Mr Sher Muhammed Solangi Entomologist Federal Minister of Health. In this meeting it was revealed that national authorities had made preparations and invited participants for the workshop in Lahore 9-13 August. This arrangement was done without the knowledge of WR or the consultant. Moreover, there was no ongoing falciparum malaria transmission in Lahore, which rendered it unsuitable for such activity. It was then decided that application of the *in vivo* test and the workshop should be held in Quetta, Balochistan, where available information indicated that cases of falciparum malaria were being reported.

Arrival in Quetta on 4 August, met by Dr Mehboob Badini Provincial WHO Operations officer, Balochistan.

On Wednesday 5 August a meeting was arranged by Dr Badini, held in Balochistan Directorate of Health and attended by:

Dr Rashid Baloch, Acting Director General of Health

Dr Mehboob Badini Provincial Operations Officer

Dr Khan Jehan, Provincial Chief Malaria Programme

Dr Yousef Bezejo D.H.O Quetta/ Provincial Coordinator for FP and PHC Balochistan

Mr Abdul Sattar Senior Malaria Superintendent

Dr Mahmood S Paracha Epidemiologist

Mr Ali Ahmed, Entomologist

Mr Sadiq Malaria Superintendent

The meeting discussed the plan to do the *in vivo* test in Quetta and selection of sentinel posts. It was agreed that the test would be done in three posts:

1: *Quetta*, Provincial HQ

2: *Kuchlak* RHC (about 24 Km North of Quetta)

3: *Dust Kumbela* Basic Health Unit (BHU). (about 30Km South of Quetta)

The posts at Kuchlak and Dust Kumbela had no laboratory facilities and no antimalarial drugs were available. Two laboratory assistants were assigned to these posts and laboratory equipment and drugs were provided by local health authorities. All laboratory assistants were then trained on doing parasite count since they had no experience in this procedure before.

In vivo test was started in all three posts in 6 August .

The *in vivo* test progressed fairly satisfactorily. Although a large number of cases recruited at HQ because they came from remote areas such that their follow up attendance was rather poor. On the other hand, in the BHU follow-up of cases was much better because the catchment area is a small village. Yet the problem in the BHU was that malaria cases were seen by a malaria superintendent because there was no Medical Officer. With its emphasis on clinical findings the new protocol requires a clinician to see the patients. Overall, this exercise did provide the workshop participants with training material and demonstrated application of the test under different settings.

A large number of cases had been screened. During the days of the test 6-13 August, 1384 blood films were done, 238 were positive, (181 *P.vivax* and 57 *P.falciparum*). In the BHU, besides recruitment of patients attending the clinic, we surveyed the village. Of 837 blood films made, 44 were positive for *P. vivax* and 13 *P.falciparum*. At the end of the workshop (day-7 of the test) about 30 cases of *falciparum* malaria were being followed. It was left to local staff to complete the test to day 14 and submit the results to Federal Ministry of Health.

2: WORKSHOP

The workshop on monitoring therapeutic efficacy of antimalarial drugs was held during the period August 11-13. The list of participants and the program attached (ANNEX II,III). In the first day a plenary session was devoted to review of malaria situation and drug resistance in Pakistan and introduction of the new protocols. In the second day participants visited sentinel posts where the test is being carried out. In the third day a plenary session was held to discuss the protocol, national plan of action, and training programme.

Provincial Plans of Action were presented by participants from the different provinces. In light of these plans the National Plan of Action included in the present report (item 6 below) was drafted, discussed and approved by the workshop. Training programme prepared by the consultant in collaboration with national workers was also presented, discussed and approved by the workshop. After discussion of the protocol, the meeting approved application of the protocol in Pakistan after some minor modifications. The proposed modifications are shown in ANNEX IV. Finally, recommendation included in the present report (item 5 below), discussed and approved by the workshop.

3 OTHER REMARKS :

The consultant had no chance to meet Director of Malaria Control Program or review the Malaria Control Program as a whole, but field application of the in vivo test and the discussions in the workshop brought up some points that are not directly related to this assignment but are worth mentioning to help improving malaria case management in Pakistan:

1: Deficiency of malaria microscopy services. In the rural hospital of Kuchlugh, for example, two doctors are working without the help of a microscopist or a microscope. If we take into account that fever is most common medical condition seen in this clinic and that both *P.vivax* and *P.falciparum* are both endemic we will not need to emphasize the importance of malaria microscopy in such a facility. Besides saving drugs, better management of cases, improvement of microscopy services will rectify conflicts in malaria data from Pakistan sometimes based on microscopically confirmed cases and sometimes on clinically diagnosed cases.

2: The need for formulation of national malaria treatment policy: During the workshop several speakers raised points related lack of such a policy in Pakistan.

3: Malaria Control Program needs to recruit nationals and train them to lead this program. At present there are nationals with long experience but they are either retired or engaged with other programs. Those currently in charge are rather new to this field.

4:CONCLUSIONS

1: Drug resistant *falciparum* malaria is present in Pakistan, both in local inhabitants and among Afghan refugees.

2: Earlier studies of the problem were conducted in a haphazard, non-systematic way.

3: Currently there is no system for continuous monitoring malaria drug resistance in Pakistan.

4:The protocol recently developed by WHO for monitoring therapeutic efficacy of antimalarial drugs against *falciparum* malaria is applicable and suitable for application in Pakistan after minor modifications.

5:RECOMMENDATIONS

1:To establish a project for continuous monitoring of susceptibility of malaria parasites to drugs in Pakistan.

2 A national project coordinator should be assigned and he/she will be responsible for training, implementation of monitoring activities and submission of an annual report on the status of susceptibility of malaria parasites to drugs.

3:Provincial health authorities should be urged to facilitate implementation of monitoring activities by availing their staff and material support.

4: A national workshop should be held (possibly in February 1999 following the implementation of the proposed Plan of Action) to formulate national malaria treatment policy, to be guided by results of susceptibility testing. .

5: The Federal Ministry of Health should provide drugs and supplies of standard quality for running the in vivo test.

6: Recruitment and training of national staff for senior management level of the Malaria Control Program.

6:PLAN OF ACTION:

Activity	By whom	Completion Dates
Assigning a national coordinator. Selection of training team	Malaria Control Program	15 September 1998
Selection of sentinel posts Identification of staff for sentinel posts	Provincial Directorates of Health /National Coordinator	30 September 1998
Training: Punjab (2 courses) NWFP(2 courses)	Training team	31October 1998
Training : Sindh (2 courses) Balochistan (2 courses)	Training team	30 November 1998
Conduction of <i>in vivo</i> test in sentinel posts	Provincial Directorates of Health	End of December 1998
National Follow-up Workshop	Malaria Control Program	January 1999

7:ACKNOWLEDGEMENTS:

The success of this mission depended much on the continuous support of Dr Barzgar, WHO representative in Pakistan and Dr Mehboob Badini ,WHO Operations Officer in Balochistan..Gratitude and appreciation are also due to Dr Khan Jehan, Malaria Chief, Balochistan Province who accompanied me in the various field trips . Participation of Dr Imtiaz Shah , with his life-time experience provided the workshop with a valuable source of information. Thanks are also due to Dr Mehmood Pracha Epidemiologist for his great help in running the field test and follow up of cases. My counter-part Dr Triq Zulqarnain was very helpful in management of the workshop and field work.

ANNEX II

LIST OF PARTICIPANTS:

WHO

Dr Mehboob Badini WHO Balochistan
 Dr Asad Ali Abro Operations Officer (PHC), WHO Sindh, Karachi
 Mr M. Isamatullah Chaudhry WHO Punjab

NIH ISLAMABAD:

Mr Sher Muhammad Solangi , Senior Scientific Officer (Entomology)
 Mrs Ghazala Taqir Nadeem, Senior Research Officer

PUNJAB:

Dr Tariq Zulqarnain Epidemiologist (**Facilitator**)
 Dr Imtiaz Shah (**Facilitator**)
 Dr Abdul Rasheed Khan, Director Health services(CDC) , Govt Punjab Lahore.
 Dr Mohsen Naqvi Regional Director Malaria Control , Punjab
 Mr Salim Rana , Parasitologist , Punjab .

SINDH

Dr Khalid Mehmood, Associate professor of Medicine, Dow Medical College ,
 Karachi
 Dr Nusrat Ali , Registrar, Department of Medicine, Dow Medical College , Karachi.
 Mr Shagan Lal, Senior Microscopists, District Thatta, Sindh
 Mr Nirbhadas , Senior microscopist, District of Sandhar Sindh.

BALUCHISTAN:

Dr Khan Jehan, :Chief Malaria Control Programme, Balochistan Province (**Facilitator**)
 Dr Ghulam Sawar ,Assistant Professor Pathology Bolan Medical College Quetta
 Mr Ali Ahmed , Entomologist MCP Balochistan
 Dr Mehmood Pracha, Epidemiologist MCP Balochistan
 Mr Noor Mohamed Assistant Malaria superintendent District of Khuzdar
 ,Balochistan
 Mr Abdul Sattar, Senior malaria superintendent District of Quetta ,Balochistan

NWFP

Mr Shawkat Parvez Entomologist DGHS Peshawar
 Mr Fazle Raziq, Entomologist NWFP, Peshawar

Azad Jammu Kashmir

Mr Abdul Ghafoor Senior Microscopist, Directorate of health services (CDC) Azad
 Kashmir.
 Mr Sheikh Sajjad Hussain CDC Officer, Azad Kashmir

ANNEX IV

RECOMMENDATION REGARDING THE
 PROTOCOL FOR MONITORING THERAPEUTIC EFFICACY OF
 ANTIMALARIAL DRUGS

WHO draft protocol .” *Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Malaria Draft 28.2.97*” was reviewed by the workshop and approved for application in Pakistan after the following notes and amendments are made to suit local conditions:

- 1: There is greater tendency to do the test for 28 days , which is the duration of the extended in vivo test that had been applied in Pakistan in the past two decades. However , it was also agreed that the option of doing the 14-day test should be left open .
- 2: It has been agreed (assuming the test should be done for 28 days) that the test should be started after end of the annual transmission season to avoid re-infection.
- 3: Clinicians should be in charge of running this test since there is emphasis on clinical assessment of cases (there are about 5000 First Level Care Facilities (FLCF) in Pakistan run by Medical Officers) .
- 4: Required equipment i.e. electronic balance and electronic thermometer may difficult to obtain in the field .The use of these equipment will not be mandatory.

5: Most participants felt that the method for sample size determination as described in the protocol should be simplified. It was also clear that most of workers who would be applying the test have no background in statistics and would not be in a position to determine the sample size by themselves.

So it was felt that some simple directive about sample size should be given.

As of yet, there is no upper limit of treatment failures to be targeted by the in vivo test in Pakistan. According to the standard protocol this information is crucial for deciding sample size and interpretation of results . It was agreed that for the time being the test should be run to detect communities that have prevalence of resistance $\geq 25\%$. For $P_a=0.1, \alpha=.05, \beta=0.2$ a sample of 16-42 cases would yield results for detection of this level of resistance using the Double Lot Quality Assurance Sampling procedure used in the protocol. Thus it was concluded that as a general directive in each sentinel post the round figure of 50 cases would be the target sample size. This is not a great departure from previous practice in Pakistan of selecting 30 cases from each village , increased to 50 cases to make up for cases lost to follow-up. $\alpha\beta$

6: Editorial corrections suggested: page 6 (of WHO /TDR draft 28.2.1997)

- line3 from below : ‘Absence of history...., should read ‘**Presence** of history...’
- line2 from below : ‘Absence of skin...., should read ‘**Presence** of skin ...’

ANNEX V

**SHORT COURSE FOR TRAINING FLCF WORKERS IN PAKISTAN ON
CONDUCTION OF *IN VIVO* TEST FOR MONITORING
SUSCEPTIBILITY OF
PLASMODIUM FALCIPARUM TO DRUGS**

1: JUSTIFICATION:

Treatment of malaria should be based on accurate information about susceptibility of the parasites to drugs. Workers in First Level Care Facilities (FLCF) can be trained to conduct the standard *in vivo* test and submit the results as part of routine malaria information.

2: OBJECTIVES:General Objective :

To train FLCF workers on conduction and interpretation of the standard *in vivo* test .

Specific Objectives:

A: By the end of this training course the participant **medical officer** should be able to

- 1: Identify cases of severe and complicated malaria
- 2: Select cases for the *in vivo* test based on standard inclusion and exclusion criteria
- 3: Define the terms Early Treatment Failure , Late Treatment Failure and Adequate Response in the context of the *in vivo* test.
- 4: Fill the standard forms for the *in vivo* test
- 5: Tabulate and interpret the results of the *in vivo* test.

B: By the end of this training course the participant **microscopist** should be able to

- 1: Identify *P. falciparum* and *P. vivax* in thick and thin blood films.
- 2: Do malaria parasite count.

3: INTENDED TRAINEES:

Medical officers in FLCF units

Microscopists in FLCF units

4 :RESOURCES NEEDED:

Training Team :

Senior Instructor: clinician well experienced
in the subject.

Microscopist.

Blood collection technician

Teaching Materials : copies of the standard protocol

Equipment and Supplies : as listed in standard
protocol

5:DURATION: 3 days

6: DATES:

Punjab 2 courses October 1998

NWFP: 2 courses October 1998

Sindh: 2 courses November 1998

Balochistan : 2 courses November 1998

