CHAPTER Vi

ANNOTATED BIBLIOGRAPHY

1. **A.M.J. Oduola, G.O. Omitowoju, A. Sowunmi, M.T. Makler, C.O.Falade, D.E.Kyle, F.A.Fehintola, O.A.T. Ogundahunsi, R.C. Piper, B.G. Schuster, and W.K. Milhous 1997. *Plasmodium falciparum*: Evaluation of Lactate Dehydrogenase in Monitoring Therapeutic Responses to Standard Antimalarial Drugs in Nigeria. *Experimental Parasitology* 87, 283-289.**

The study purposed to evaluate the response of infection to treatment by microscopic examination of thick and thin blood smears, clinical symptoms, and level of pLDH activities in blood products. Three hundred fifty-three patients were recruited as part of two studies during the 1994 and 1995 malaria seasons. The studies were conducted in Ibadan, Nigeria. Each patient with confirmed *P. falciparum* infection was enrolled and randomized to one of four groups for treatment with standard dosages of antimalarial drugs. Response of infection to treatment in each patient was monitored for 28 days. Thick and thin blood films were prepared from finger-prick blood samples during the follow-up visits. Packed cells, plasma and whole blood were used for determination of pLDH activities. The Malstat reagent (Flow Inc., Portland, OR) and an immunoenzymatic capture technique were used. The end point reaction was determined by spectrophotometer at 650nm. Non infected Nigerian volunteers and

American volunteers were used as a negative control and a bacteria-expressed *P. falciparum* LDH was used as a positive control. The level of enzyme activities varied with parasite density and blood products evaluated. There is a consistent relationship between patent infection and pLDH activities that could easily be determined in whole blood and packed cells but not plasma from the patients. The pLDH activities in samples with significantly gametocyte count could have been misconstrued for active infection if clinical symptoms were not taken into consideration.

2. A.H.Moody, S.M.John, A.Sudarsanam, U.Sitaram 1998. Evaluation of OptiMAL, a dipstick tests for the diagnosis of malaria. *Annals of Tropical Medicine & Parasitology*, Vol. 92, No. 5, 621-622.

This study conducted to examine 101 blood samples from patients who were diagnosed as malaria cases at the Christian Medical College & Hospital, Vellore, Tamil Nadu, India. The OptiMAL dipsticks were performed from blood samples that were stored at -70°C for up to 6 months. The OptiMAL results compared to microscopy demonstrated the sensitivity of 94% in *P. falciparum* detection and 98% in *P.vivax* detection.

Not surprisingly the OptiMAL could not detect mixed infections (7 samples) neither the two cases having only *P. falciparum* gametocytes (2/34). The author comments that the OptiMAL could be the alternatives where laboratory facilities are poor. Besides, timing used to perform the OptiMAL dipstick was much less than the microscopy.

3. **Quintana M., R. Piper, H-L Boling, M. Makler, C. Sherman, E. Gill, E. Fernandez, S. Martin 1998. Malaria Diagnosis by Dipstick Assay in a Honduran Population with coendemic *Plasmodium falciparum* and *Plasmodium vivax. American Journal of Tropical Medicine and Hygiene., 59 (6),* 868-871.**

The pLDH dipstick assay was evaluated in a Honduran hospital and field population. The hospital study was conducted in May 1997 at the Honduran Ministry of Health hospital in Trujillo, La Ceiba, Atlantida. Consenting patients referred to the hospital laboratory with a presumptive diagnosis of malaria were recruited into the study. In the field study, blood samples were collected from La Ceibita, Tocoa, Colon visited in November 1996. Blood was obtained from the same fingerstick for the thick blood film, pLDH dipstick assay, and PCR analysis. The average parasitemia was approximately 591/cu.mm in hospital samples. The sensitivity of the pLDH assay was 100% and the specificity was 95% compared with microscopy in hospital samples. For field samples, the average parasite density was around 167 /cu.mm. The sensitivity was 100 % for parasite densities > 88/cu.mm. but decreased to 78% for < 88/cu.mm. These data showed that the pLDH dipstick assay is as sensitive as thick film microscopy in the diagnosis of malaria when the parasite density > 88/ cu.mm. In a clinical laboratory hospital in a malaria endemic area, the parasite densities of symptomatic patients were high enough for the dipstick to perform at a sensitivity of 100 % and a specificity of 95%. For the species diagnosis, the data from the study seems to underscore to evaluate (there were all 13 *P. vivax* positive in hospital samples). Additionally, the explanation

for the negative PCR results in four cases positive by the pLDH dipstick assay is unknown. Also mixed infections remains a problem in pLDH dipstick assay.

4. **C J Palmer, Lindo JF, Klaskala WI, Quesada JA, Kaminsky R, Baum MK, Ager AL. 1998 Evaluation of the OptiMAL test for rapid diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* malaria. *Journal of Clinical Microbiology* Jan; 36 (1): 203-206.**

This trial evaluation of the OptiMAL test was designed to assess its effectiveness in differentiating malaria during a malaria outbreak in Honduras. A total of 202 patients with malaria like symptoms were included into this study that evaluate OptiMAL against microscopy. Symptomatic patients were treated immediately with chloroquine by local health staff prior to diagnosis on site. Unlike the other studies, 82% (79 of 96) of total cases in this trial are *P. vivax* and 18%(17 of 96) are *P. falciparum.* Mentioned in the study that OptiMAL can detect mixed infection by looking at the intensity of the band on dipstick, this statement later found it to be unlikely to rely. The results obtained were sensitivity 94% and 88% and specificity 100% and 99% respectively, when compared to traditional blood films for the detection of *P. vivax* and *P. falciparum* infections. Sensitivity in detecting *P. vivax* was only 40% when parasites were present at less than 100μL of blood. Comparison of OptiMAL, ParaSight-F, and ICT Malaria P.f. for detection of *P. falciparum,* the results obtained were underscored (17 microscopically confirmed). Commented by the author that the common problem in malaria quantification is the different laboratories base parasite densities on leukocyte counts, which vary between 1,000 and 10,000/μL of blood.

Other laboratories determine parasite density by using erythrocyte formulations. The use of various methods to determine levels of malaria parasitaemia is turning into a major problem, as it makes comparisons of test results from different malaria researchers difficult is true.

5. **Jelinek T, Grobusch MP, Schwenke S, Steidl S, von Sonnenburg F, Nothdurft HD, Klein E, Loscher T. 1999 Sensitivity and specificity of dipstick tests for rapid diagnosis of malaria in non-immune travelers.** ***Journal of Clinical Microbiology.,*** **Mar; 37 (3): 721-723.**

The prospective multi-center study conducted in non-immune German travelers returning from malaria endemic areas. This study evaluated HRP-2 dipstick (ICT Malaria P.f.) and pLDH dipstick (OptiMAL) against thick and thin blood films.

If discordant results between microscopy and one of the dipstick tests occurred, a PCR method was used to confirm the presence of plasmodial DNA. From 231 patients, 53(23%) were microscopically confirmed with *P. falciparum,* 13(5.6%) with *P. vivax.*

For *P. falciparum* infections, both dipsticks provided good sensitivity and specificity. ICT Malaria Pf performed with 92.5% sensitivity and a specificity of 98.3% in comparison, OptiMAL showed a sensitivity of 88.7% and a specificity of 99.4%

Apart from this a false negative from the prozone phenomena was also occurred in both dipsticks. One sample with a very high parasitaemia of 20,000/μL was repeatedly negative in both tests. Regarding the detection of *P. vivax* by OptiMAL (sensitivity 61.5%; specificity, 100%) clearly, a large set of patients with *P. vivax* infections needed to investigate before conclusion. From this study, if consider about the false negative from prozone phenomena, it should be emphasized that *P. falciparum* malaria, a potential fatal disease, must not be missed because of a false negative dipstick test.

6. **Bualombai, K Chongpuong, S Konchom, S Rachamanee, A Thongpratum, 1999. Validation of OptiMAL Test for Diagnosis of Malaria in an Endemic Area: a Pilot Study.** ***Communicable disease Journal*** **Vol.25 No. 2 Apr-Jun 1999.**

This pilot study conducted in 94 suspected cases attending five malaria clinics and one mobile-malaria clinic under responsibility of the Center of Vector-Borne Disease (VBDC), Kanchanaburi Province. This study compared microscopy (Thick blood film stained with Giemsa) and the OptiMAL. The OptiMAL results (Sensitivity, Specificity) were as good as microscopy performing in the field. However, the sample size of this study was very small with only 14 cases of *P. falciparum* infection and 10 cases of *P. vivax* infection and only thick blood film microscopy were used as a gold standard. The author suggested a large-scale trial before implementation to field use.

7. **C J Palmer, L Validum, J Lindo, A Campa, C Validum, M Makler, R R. Cuadrado, A. Ager 1999. Field evaluation of the OptiMAL® rapid malaria diagnostic test during anti-malaria therapy in Guyana.** ***Transactions of the Royal Society of Tropical Medicine and Hygiene*** **93, 517-518.**

The study conducted in Georgetown and Mahdia, Guyana. Twelve adult patients infected with *P. falciparum* were recruited in the study that purpose to evaluate the performance of OptiMAL against gold standard in short term therapeutic monitoring. The result of the study showed OptiMAL has 100% of the Level of agreement (with microscopy) on day 0, while the Level of agreement on day 3 and 5 were 45% and 83% respectively. For the OptiMAL positive/ blood film negative, the explanation is that most parasites had been killed by the medication and that the few remaining parasites were present at levels below microscope detection. The OptiMAL negative/ blood film positive may have been due to death of the parasites, so they were no longer producing pLDH and would not be detected by OptiMAL but were not yet cleared from the blood stream. The author concluded that OptiMAL is an excellent diagnostic tool and has the ability to monitor the results of patient antimalarial treatment. However, regarding to mean of level of parasites in this study, which was very low (day 0 = 175 (range 2-690), day 3= 6.67 (0-60) and day 5 = 0.33 (0-5).

8. **Hunt Cooke A, P.L. Chiodini, T. Doherty, A.H. Moody, J Ries, M. Pinder 1999. Comparison of a Parasite Lactate Dehydrogenase-Based Immunochromatographic Antigen Detection Assay (OPTIMAL®) with Microscopy for the Detection of Malaria Parasites in Human Blood**

Samples. ***American Journal of Tropical Medicine and Hygiene.*** **60(2), 173-176.**

In this study, the 409 patients more than one year of age attending the Outpatients' clinic, MRC (Fajara, The Gambia) during November 1996. The patients with fever or history of fever and a suspected diagnosis of malaria were recruited into the study that aimed to evaluate the performance of the OptiMAL as initial diagnosis.

The OptiMAL test was subjected to a stringent comparison with the gold standard, the microscopists with substantial experience. Unlike other studies, a negative control sample taken from an individual who had no history of malaria for three years was also tested. The treatment was based on the result of microscopy followed the current Gambian National guideline for the management of malaria. The sensitivity of the test was 100% but decreased remarkably below a parasitaemia of 0.01% (500 parasites/μL). The remark from the study were first, 90% of the samples from this study who were found *P. falciparum* showed parasitaemia ≥0.01% so the OptiMAL still have detected a major malaria cases with a good specificity in this setting. Therefore, in non-immune population (e.g. Thai-Burmese border) the lack of sensitivity of the test below this level is a disadvantage. Second, because *P. vivax* is not endemic in Gambia so this study had few cases of *P. vivax* consequently the findings could not demonstrate the diagnosis characteristics of *P. vivax*. Third, the OptiMAL test was evaluated in an air-conditioned laboratory, rather than in the field conditions.

9. **David J. Fryauff, Purnomo, Mochammad A. Sutamihardja, Iqbal R.S. Elyazar, Ika Susanti, Krisin, Budi Subianto, and Harijani Marwoto (2000).**

Performance of the OptiMAL® assay for detection and identification of malaria infections in asymptomatic residents of Irian Jaya Indonesia. ***American Journal of Tropical Medicine and Hygine.*****, 63(3,4), 139-145.**

Unlike most of the OptiMAL studies, which evaluated the diagnostic characteristics, this study evaluated the screening capacity of the OptiMAL test. The purposes of this study were to determine the lower limits of sensitivity as well as the specificity and stability of the OptiMAL test by compared its performance to expert microscopy for detection of *P. falciparum* and *P. vivax* malaria in an active-case detection screening of asymptomatic population living in Irian Jaya, Indonesia. The rationale was to avoid bias from knowledge of clinical illness and to permit assessment of the new test against a range of light, naturally occurring, and genetically diverse malaria infections. The assay was performed on 276 native Irianese with life-long malaria exposure and 232 Indonesian transmigrant who had lived in Irian Jaya for 12 to 30 months. Subjects screened by the two methods reported no malaria-like illness at the time of blood sampling. To evaluate the stability of the OptiMAL assay, one technician performed all tests and reading in the field. Another technician reread the same OptiMAL strips 5 months later. PCR was applied to a sample of discordant microscopy/OptiMAL results to validate the accuracy of consensus microscopy. The overall GM parasitaemia was 377 parasites/μL. Sensitivity of OptiMAL for detection of any malaria infection in the combined populations was 60% and 70% respectively and specificity was 97% and 89%. There were no significant between-reader differences

($P > 0.17$). Most cases identified by microscopy as *P. falciparum* were graded as negative or *non-falciparum* by both OptiMAL readers. OptiMAL false negatives as well as misidentifications were related to low parasitaemia (< 500/μL). At the level of 500-1,000 parasites/μL, the sensitivity was 88-92%. This is useful in primary symptomatic cases that the parasitaemia level usually between 500-1,000 parasites/μL or higher. In summary although the OptiMAL demonstrated the satisfying results at a symptomatic parasitaemia level but to use OptiMAL as an epidemiological screening tool is not recommended because in the range of asymptomatic parasitaemia studied, it was found markedly less sensitive than expert microscopy for reliable detection or species discrimination.

10. Moody A, Hunt-Cooke A, E. Gabbet, P. Chiodini 2000. Performance of the OptiMAL malaria antigen capture dipstick for malaria diagnosis and treatment monitoring at the Hospital for Tropical Diseases, London 2000. *British Journal of Hematology* 109. 891-894.

Blood samples of 636 patients attending the Hospital for Tropical Disease (HTD) with symptoms suggestive of malaria were examined for malaria parasites by thick and thin blood films and OptiMAL test. The patients included both semi-immune and non-immune individuals. Patients whose blood contained *P.falciparum* were admitted for therapy and daily blood samples were collected to follow the parasitaemia. In this study, the sensitivity and specificity of OptiMAL for the diagnosis of *P. falciparum* parasites from untreated patients was 95% and 100% respectively.

For *P. vivax,* the sensitivity was 96% and a specificity of 100 % was obtained. Fifty-one of the cases with *P. falciparum* infection were followed daily, parasitaemias were estimated and OptiMAL performed on each sample. The reduction in percentage positivity of OptiMAL on samples collected during treatment compared with that obtained for initial diagnostic samples reflected the decrease in pLDH activity as the viability of parasites declined with therapy. The sensitivity and specificity of OptiMAL reported in this study were very high for *P. falciparum*, even against the expert microscopy of a tropical reference center. The sensitivity for gametocytes only was lower than that for asexual parasites. At a given parasitaemia, the sensitivity of OptiMAL is lower after the initiation of treatment than it would be before treatment at the same parasitaemia. This support the view that OptiMAL detects pLDH produced by viable parasites and the ability to follow its decline in sequential samples from patients during treatment is potentially useful in following clinical cases.

11. S. Srinivasan, A. H. Moody and P. L. Chiodini 2000. Comparison of blood-film microscopy, the OptiMAL dipstick, Rhodamine-123 fluorescence staining and PCR, for monitoring antimalarial treatment. *Annals of Tropical Medicine & Parasitology*, Vol. 94, No. 3, 227-232.

This article compared blood-film microscopy, the OptiMAL, Rhodamine-123 fluorescence staining, which detects only the viable parasites and PCR. This pilot study of 17 patients with *Plasmodium falciparum* infection, admitted to the Hospital of Tropical Diseases, London conducted for the purpose of both diagnostic characteristics evaluation and the antimalarial treatment monitoring. The result of testing on the initial

day (as to evaluate the diagnostic characteristics) was good with a sensitivity of 100% compared to microscopy. The results of testing the sequential blood samples (as to evaluate the antimalarial treatment monitoring) were in between a Rhodamine-123 and a microscopy. From the study, R-123 demonstrated the quicker response to the antimalarial treatment followed by the OptiMAL, a microscopy and PCR respectively. Since R-123 is difficult to perform in the developing countries, the author suggested that the OptiMAL provided the potential alternatives for use in monitoring antimalarial treatment.

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A.M.J. Oduola, G.O. Omitowoju, A. Sowunmi, M.T. Makler, C.O.Falade, D.E.Kyle, F.A.Fehintola, O.A.T. Ogundahunsi, R.C. Piper, B.G. Schuster, and W.K. Milhous 1997. *Plasmodium falciparum*: Evaluation of Lactate Dehydrogenase in Monitoring Therapeutic Responses to Standard Antimalarial Drugs in Nigeria. *Experimental Parasitology* 87: 283-289.

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