Original Article

Role of rapid diagnostic tests for guiding outpatient treatment of febrile illness in Liaquat University Hospital

Salma Shaikh[1], Shazia Memon[2], Hafeezullah Memon[3], Imran Ahmed[4]

ABSRTACT

Objectives: To assess the validity /strength of clinical diagnosis of Malaria on the basis of IMNCI algorithm by slide microscopy (gold standard) and to compare the effectiveness of Rapid Diagnostic Test (RDT)against slide microscopy.

Methods: It is a descriptive cross sectional study of 6 month duration conducted at Pediatric Outpatient Department LUH Hyderabad from June-Dec. 2010. Sample of 400{the minimum required sample was 385 with malaria prevalence 5% (0.05) with margin of error of 3% (0.03, frequency vary from 2—8 % among different studies)} febrile children under 5 years classified as Suspected Clinical Malaria according to algorithm of IMNCI were included; The operational definition for Suspected Clinical Malaria was; fever for more than 2 days with no runny nose, no measel rash and no other cause of fever. Hyderabad was considered as low risk area. Rapid diagnostic test (RDT) and slide microscopy were done, and only confirmed cases were treated according to current guidelines given by National Malaria Program/updated IMNCI.

Results: Total 2000 patients under 5 years presented with fever and were evaluated. From 2000 cases 20% (400) were diagnosed as suspected clinical Malaria according to IMNCI algorithm; and only 40 cases (10%) have shown positive results for malaria parasite on slide microscopy and 38 cases on RDT. Regarding the plasmodium species 70% were vivax and 30% were falciparum. As regards the effectiveness, RDT has shown 95% sensitivity for the detection of plasmodium antigens in the febrile clinically suspected cases of malaria.

Conclusion: Prompt and accurate diagnosis of malaria is needed for implementation of appropriate treatment to reduce unnecessary anti-malarial prescription. RDT is as effective as slide microscopy for the diagnosis of malaria especially in resource poor countries.

KEY WORDS: Malaria Diagnosis, Rapid Diagnostic Test (RDT), Slide Microscopy.

doi: http://dx.doi.org/10.12669/pjms.295.3937

How to cite this:

Shaikh S, Memon S, Memon H, Ahmed I. Role of rapid diagnostic tests for guiding outpatient treatment of febrile illness in Liaquat University Hospital. Pak J Med Sci 2013;29(5):1167-1172. doi: http://dx.doi.org/10.12669/pjms.295.3937

1. Dr. Salma Shaikh,
Professor of Pediatrics,
2. Dr. Shazia Memon,
Assistant Professor of Pediatrics,
3. Dr. Hafeezullah Memon, FCPS,
Resident of Pediatrics,
4. Dr. Imran Ahmed, FCPS,
Resident of Pediatrics,
1-4: Liaquat University of Medical & Health Sciences (LUMHS),
Jamshoro, Sindh, Pakistan.

Correspondence:

Dr. Shazia Memon,
B-16 Hesco Colony, Kotri Road, Hussianabad, Hyderabad, Pakistan.
E-mail: shazia.memon@lumhs.edu.pk

* Received for Publication: June 10, 2013
* First Revision Received: July 10, 2013
* Second Revision: July 11, 2013
* Final Revision Accepted:* July 15, 2013

INTRODUCTION

Malaria is the major public health problem in Pakistan. The disease is endemic both Plasmodium falciparum and Plasmodium vivax are widely distributed and disease threatens millions of people due to conditions conducive to the spread of disease.[1] Every year 300–500 million clinical episodes of malaria results in 2 million deaths worldwide. A vast majority of those took place in sub-Saharan Africa, and many involve children aged <5 years.[2] Malaria accounted for 18% (precision estimate: 15.8–20.2%) of child deaths.[3] The more specific malaria diagnostic would better identify those children without malaria who

need more careful examination to determine an alternative diagnosis. Delay in the proper diagnosis and treatment can progress to severe malaria in a matter of hours and mortality rates can reach 30% even among those hospitalized.[1] Pakistan health management information system (HMIS)'s 2006 reports malaria as the second most frequently reported disease.[4] Although at aggregate level the prevalence of malaria in Pakistan is moderate, there is variation in prevalence from province to province. In 2005, falciparum malaria constituted 33% of reported confirmed malaria cases, this figure decreased to 24% in 2008, with 40% of cases from Baluchistan province.[5] Pakistan launched Malaria eradication campaign with the help of WHO in 1960, but eradication could not be achieved because of socio- economic and epidemiological factors. In 1975 strategy switched from eradication to control when malaria control interventions was integrated into the primary health care system.[6]

The Millennium Development Goals (MDGs), include a target in Goal 6: "to have halted by 2015 and begun to reverse the incidence of malaria and other major diseases."[7] Following the launch of the MDG and international initiatives like Roll Back Malaria (RBM), there has been an upsurge in support for malaria control. Pakistan's national strategy for control of malaria has been developed within the RBM framework in 2007 and early diagnosis and appropriate treatment, multiple prevention and epidemic preparedness and behavioral change communication were included as strategic priorities.[8]

At present malaria is diagnosed on clinical grounds alone, without diagnostic tools. Clinical algorithm of Integrated Management of Childhood Illnesses (IMCI) algorithm, is commonly used to diagnose children presenting with fever, but is relatively non-specific.[9] In 2006 WHO estimates an annual malaria burden of 1.6 million cases for Pakistan, but lady health worker prescribed over 4.4 million doses and the prescription of these drug by the private sector amounted to 70 million doses.[10] The over treatment and development of resistance to newer drugs can only be prevented by prescribing anti-malarials only to confirmed cases of malaria.

The essential points of the latest national malaria program are: Treatment based on clinical grounds alone should be reduced by making available RDT or Microscopy. Artemisinin based combination therapies (ACT) should be introduced for uncomplicated falciparum malaria. Chloroquine and primaquin therapy be used for vivax malaria.[6]

To confirm the diagnosis, blood-slide microscopy is the primary diagnostic tool utilized in resource-limited settings. Expert microscopy is highly sensitive and specific, and allows differentiation of the four malaria parasite species capable of infecting humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae. However, consistent and dependable microscopy requires trained technicians, electricity, well-maintained microscopes and time (one hour to produce results).[11] Alternatively Polymerase chain reaction (PCR) and malaria rapid-diagnostic tests (RDTs) are two other methods. PCR is highly sensitive and can differentiate malaria species. However, the cost, time, training and laboratory infrastructure requirements make this an unrealistic tool for widespread use in resource-limited settings.[12]

Hand held immuno-chromatographic rapid diagnostic tests (RDTs) have been recognized as an ideal alternative method to slide microscopy. Many RDTs are currently available and are being increasingly used in the field. Current RDTs identify P. falciparum-specific histidine-rich protein II (HRP2), parasite-specific lactate dehydrogenase (pLDH) or pan-specific aldolase.[10] Results of rapid diagnostic tests are rapidly available, less liable to the theoretical risk of being falsely negative due to parasite sequestration, and visible to both prescriber and patient.[11] Initial data indicates its cost effectiveness because improved diagnostics, coupled with effective treatment, would result in 1,800,000 adjusted lives saved. This effect would occur both directly through improved case detection and indirectly through conservation of resources, slowed development of drug resistance and improved differential diagnosis of febrile children[13]. So rapid diagnostic tests for malaria is reasonable in an era of more expensive drugs such as artemisinin combination treatment, and their use could result in significant savings, especially in areas of low transmission. [14]

The rationale of study is to know the actual frequency of Malaria from clinically suspected Malaria. This study addresses an important area of case management practices. The outcome of the study would be helpful for further improving the diagnosis and treatment of malaria especially in children <5 years of age.

The Objectives of our study were to validate the clinical diagnosis of Malaria with slide microscopy (gold standard) and to compare the effectiveness of RDT against slide microscopy.

METHODS

This community based descriptive cross sectional study was conducted from June to Dec 2010 at outpatient department of paediatrics LUMHS Hyderabad. Children under 5 year of age who presented with fever and classified as Suspected Clinical Malaria according to IMNCI algorithm were enrolled. The operational definition for classifying as Suspected Clinical Malaria was; fever for more than 2 days with no runny nose, no measel rash and no other cause of fever.[9]

Lack of consent and incomplete data constituted the exclusion criteria. Medical history, socio-economic and demographic data were recorded on study proforma Around 400 patients were recruited (385 estimated sample with 5% prevalence of malaria). We estimated the sample size with help of WHO manual "Sample Size Determination in Health Studies". Our anticipated frequency of malaria was 5% (0.05) with margin of error of 3% (0.03, frequency vary from 2—8 % among different studies) with 95% confidence interval.[15] After enrollment the diagnosis was confirmed by slide microscopy thick and thin smears. RDT was also applied on all cases to measure its effectiveness. The research team comprised of one research officer, one postgraduate student and malaria technician were trained by conducted one-week residential training workshop in pediatric department. Standard operating procedures for: 1) finger prick for collection of blood, 2) thick/thin blood smear preparation, 3) staining smears, 4) blood smear reading, 5) preparation and reading of RDT were included in training.

Each film was graded as positive (asexual malaria parasites seen) or negative (no malaria parasites seen) based on the inspection of 200 fields of the thick smear. The numbers of asexual and sexual parasites were counted in the same fields until 500 white blood cells (WBC) were observed. The parasite density was estimated assuming 8,000 white blood cells/µl as total leucocytes count in the peripheral smear. The thin smear was useful in species identification. The MP technician was blind of the RDT results. The choice of RDT device (NOVA, Pakistan specific only to detect vivax and falciparum) was based on its stability, low cost, reported high sensitivity (97%) and moderate specificity (88%) in controlled trials. The test preparation and interpretation was done following manufacturer's instructions. Each test was read by research officer and postgraduate.

All patients with positive test results (slide or RDT) were immediately treated according to national malaria guidelines on the same day of visit. Patients with negative results were referred back to Medical officer in the pediatric out-patient department for assessment and an appropriate treatment for possible alternative diagnosis of their febrile illness.

For Statistical analysis data was double-entered and validated in SPSS version 16 software. The sensitivity, specificity, PPV and NPV of RDT were calculated with slide microscopy as gold standard. Sensitivity was calculated as the proportion of positive test results of RDT obtained among Slide microscopy positive cases, and specificity was calculated as the proportion of negative test results of RDT among slide microscopy negative cases. PPVs and NPVs were calculated as the proportion of true-positive results among all positively reacting samples and as the proportion of true negative results among all negatively reacting samples, respectively. Accuracy of each test was calculated overall with 95% confidence interval (CI).

RESULTS

During this period around 2000 under 5 year patients presented with fever at out-patient pediatric department LUH Hyderabad and it was considered low risk area for malaria. From 2000 cases only 20% (400) were diagnosed as suspected clinical Malaria according to IMNCI algorithm. Distribution of sex and different age groups were shown in Table-I and Districts of positive cases and plasmodium species is shown in Table-II.

From 400 cases only 40 cases (10%) have shown positive results for malaria parasite

Table-I: N. 400.

Sex:	*No. of cases*	*Percentage*
Females	260	66%
Males	140	34%
Age groups:		
2-6 months	78	19%
7-12 months	74	18%
1-5 years	248	63%

Table-II: Districts of positive cases N: 40.

District	*Falciparum*	*Vivax*	*Total*
Hyderabad	8	20	28
Matiyari	4	4	8
Tando Mohd Khan	0	4	4
Total	12	28	40

Table-III: Sensitivity & specificity.

	Malaria (MP+ve)	*Malaria (MP-ve)*	*Total*
RDT Positive	38	30	68
RDT Negative	02	330	332
Total	40	360	400

on slide microscopy and RDT. Regarding the plasmodium species 70% (28) were vivax and 30% (12) were falciparum. Except only two cases all the cases positive on slide microscopy has also shown positive results on RDT. Regarding the effectiveness, RDT has shown 95% sensitivity for the detection of plasmodium antigens in the febrile clinically suspected cases of malaria. Effectiveness of RDT with sensitivity and specificity is shown in Table-III.

DISCUSSION

The Study was conducted in the outpatient department of paediatrics LUMHS Hyderabad from June to December 2010. All febrile children under 5 years of age classified as suspected clinical malaria confirmed slide microscopy, and also the effectiveness of RDT was measured by using expert microscopy as gold standard. The sensitivity (95%), specificity (91.6%), PPV (0.55%) and NPV (99.3%) of RDT were similar to that reported elsewhere.[16]

Overall, the performance of RDTs was similar to that of microscopic analysis performed by an experienced microscopist. Compared to microscopy, RDT specificity relative to that of microscopy was lower (91.0%) is similar to other studies.[13,16,17]

Our study has very low PPV which is similar to other of other studies.[11,13] The low PPV is due to the fact that RDT detect the antigens but not the parasite as slide microscopy, and antigens may persist in the serum for couple of weeks even after successful treatment giving false positive results.[17] But RDT sensitivity was excellent (95.%) and an excellent NPV of 99.5%. These encouraging results justify using RDTs to diagnose malaria in areas that are most in need of low-cost diagnostic techniques. The risk of a false-negative RDT result depends on several factors: the RDT itself (brand and even lot variation, including performance in practice) and malaria species, density, and background prevalence. Well-performed laboratory studies have shown RDT sensitivities to be generally same.[18]

B Jorkman and colleagues conducted a cross-over clinical trial of symptom-based clinical diagnosis (CD) versus CD plus RDT in four primary health care facilities in Zanzibar. The use of RDT had a major impact on clinical decision. The prescription rate of antimalarial treatment in the CD + RDT group was half that observed in the CD group (42% versus 84%)[19] There is great debate on whether or not presumptive clinical diagnosis of malaria in under five years should be abandoned.

Some scholars argued to move to laboratory confirmed (RTD based) diagnosis for younger children.[20] While Mike English and colleagues thought the sub-Optimal sensitively of RDTs in routine use increases the risk of missing true malaria case.[19] The risk of missing a malaria case due to a false-negative test is substantially smaller than the risk of the patient dying due to another severe disease because of the focus on malaria.[20] The risk of a false-negative test and its potential consequences have recently been evaluated thoroughly in Uganda (using microscopy)[17] and in Tanzania (using RDTs),[16] and the safety of not treating malaria-negative children confirmed.

Regarding the feasibility of RDT it should have good sensitivity, require minimal training and equipment, and retain accuracy even after extensive storage under tropical conditions. All these characteristic are met by the new generation of RDTs. Two meta-analyses have clearly showed that the performance of RDTs is comparable to that of expert microscopy.[21,22] According to our latest national malaria guidelines it is the time to switch from presumptive treatment to laboratory-confirmed diagnosis and treatment. But large-scale deployment of RDTs is a great challenge that requires theoretical and practical training, regular supervision, and sustained financial mechanisms to ensure constant availability.

Regarding the practicability the research officer learnt to use RDTs correctly with relative ease, confirming that the test are simple to perform is similar to other studies.[11,13] The estimated sensitivity (>100 parasites / ul of blood) is in line with WHO recommendations [12]

The use of microscopy has been tried in various health care settings, but is associated with problems of logistics, sustainability, and quality control. The development of rapid diagnostic tests (RDTs) for P. falciparum malaria offers a potential alternative in remote and poorly resourced health facilities that are beyond the reach of high-quality microscopy services.[23]

Traditionally, malaria is diagnosed using clinical criteria and/or light microscopy even though both strategies are clearly inadequate in many healthcare

settings. Hand held immuno-chromatographic rapid diagnostic tests (RDTs) has been recognized as an ideal alternative method for diagnosing malaria. However, additional and larger studies are needed, in different malaria epidemiological settings and at different health care levels and that have longer follow-up.

CONCLUSION

Our results showed that RDTs had same sensitivity and specificity compared with routine microscopy and may have an important role in malaria case management. Slide microscopy is gold standard but it requires expert personnel, electricity, microscopy and time consuming (01 hour) . RDT is 95% specific to detect plasmodium Falciparum and Vivax and easy to perform, So RDT is better alternate option for the diagnosis of malaria especially in community setup.

The RDTs if performed correctly and used by health workers to guide treatment would help to prevent unnecessary use of ACTs, which could in turn decrease the possibility of adverse events and prompt health workers to assess RDT-negative febrile patients for other diseases. Both RDT and microscopy implementation, however, require the development and implementation of training and quality assurance programs to ensure continued high performance of these tests as part of routine case management of malaria.

RECOMMENDATIONS

* Anti-malarial should only be prescribed after confirmation, as ACT is expensive and irrational use can lead to resistance which would be fatal.
* Malaria control programs could consider a combination of RDTs and microscopy for malaria diagnosis, prioritizing RDT where it is not feasible to implement good quality microscopy. the challenges of scaling up good quality microscopy as part of national malaria control programs should not be underestimated, because it requires complex and potentially costly continued training and supervision

Source of Funding: The study was funded by the Liaquat University of Medical and Health Sciences research fund. The sponsors had no part in the design, conduct, or analysis of the study.

Conflict of interests: we declared that there was no conflict of interest for any author.

Ethical approval: Ethics review committee of the Liaquat University of Medical and Health Sciences has approved the project.

REFERENCES

1. World Health Organization: World malaria report. World Health Organization, Geneva 2009.
2. Rowe AK. Estimates of the Burden of Mortality Directly Attributable to Malaria for Children under 5 Years of Age in Africa for the Year 2000: Final Report for the Child Health Epidemiology Reference Group (CHERG) (WHO, Geneva, 2004).
3. Rowe AK, Rowe SY, Snow RW, Korenromp EL, Schellenberg JR, Stein C, et al. The burden of malaria mortality among African children in the year 2000. Int J Epidemiol. 2006;35(3):691-704.
4. Khan SJ, Usman M, Abbass Y, Hussain M, Ali M. KAP study on malaria. Gomal J Med Sci. 2010;8(2):204-208.
5. Asif SA. Departmental audit of malaria control programme 2001-2005 North West Frontier Province (NWFP). J Ayub Med Coll. 2008;20:98-102.
6. E:\Pakistan_Gov_pk - The Official Web Gateway to the Government of Pakistan.htm National Program for Malaria Control.
7. UN Millennium Project 2005. Coming to Grips with Malaria in the New Millennium. Task Force on HIV/AIDS, Malaria, TB and Access to Essential Medicines, Working Group on Malaria (Earthscan, Sterling, Virginia, 2005).
8. Roll Back Malaria. WHO Eastern Mediterranean Region. Cairo, Egypt. 2002:1-14.
9. Weber MW, Mulholland EK, Jaffar S, Toedsson H, Gove S, Greenwood BM. Evaluation of an algorithm for the integrated management of childhood illness in an area with seasonal malaria in the Gambia. Bull World Health Organ. 1997;75(Suppl 1):25-32.
10. World Health Organization. Guidelines for the Treatment of Malaria. WHO/HTM/MAL/2006.1108 (WHO, Geneva, 2006).
11. Reyburn H, Mbakilwa H, Mwangi R, Mwerinde O. Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ. 2007;334(7590):403. doi:10.1136/bmj.39073.496829.
12. World Health Organization WHO/HTM/MAL/2006.1111: The role of laboratory diagnosis to support malaria disease management: focus on the use of rapid diagnostic tests in areas of high transmission. Report of WHO technical consultation. In WHO. Geneva; 2006.
13. Batwala V, Magnussen P, Nuwaha F. Are rapid diagnostic tests more accurate in diagnosis ofplasmodium falciparum malaria compared to microscopy at rural health centres? Malaria J. 2010;9:349. doi:10.1186/1475-2875-9-349.
14. Zurovac D, Njogu J, Akhwale W, Hamer DH, Larson BA, Snow RW. Effects of revised diagnostic recommendations on malaria treatment practices across age groups in Kenya. Trop Med Int Health. 2008;13(6):784-787.
15. Carley S, Dosman S, Jones SR, Harrison M. Simple nomograms to calculate sample size in diagnostic studies. Emerg Med J. 2005;22:180-181.
16. Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, et al. Over diagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ. 2004;329(7476):1212.

17. Batwala V, Magnussen P, Nuwaha F. Challenges to implementation of Artemisinin Combination Therapy policy in Uganda. Int Health. 2010;2(4):262-268.
18. Bjorkman A, Martensson A. Risks and Benefits of Targeted Malaria Treatment Based on Rapid Diagnostic Test Results. Clin Infect Dis. 2010;51(5):512-514. doi:10.1086/655689.
19. Bisoffi Z, Gobbi F, Angheben A, Van Den Ende J. Role Of Rapid Diagnostic Test In Managing Malaria. PLOS Medicine. 2009;6(4):e1000063 (www.plosmedicine.org).
20. Acremont VD, Lengeler C, Mshinda H, Mtasiwa D, Tanner M, Genton B. Time To Move From Presumptive Malaria Treatment To Laboratory Confirmed Diagnosis And Treatment In African Children With Fever. PLOS Medicine. 2009;6(1):e552 (www.plosmedicine.org).
21. Murray CK, Bennett J. Rapid Diagnosis Of malaria; Review Article Hindawi Publishing Corporation Interdisciplinary Perspectives On Infectious Diseases Volume 2009; Article ID 415953, 7 Pages doi:10.1155/2009/415953.
22. Abeku TA, Kristan M, Jones C, Beard J, Mueller DH, Okia M, et al. Determinants of the accuracy of rapid diagnostic tests in malaria case management: evidence from low and moderate transmission settings in the East African highlands. Malaria J. 2008;3:202.
23. Msellem MI, Martensson A, Rotllant G, Bhattarai A, Stromberg J, Kahigwa R, Abdullah Ali1, Anders Bjorkmanl. Influence of rapid malaria diagnostic test on treatment and health outcome in fever patients, Zanzibar—A crossover Validation. PLOS Medicine. 2009;6(4):e1000070 (www.plosmedicine.org).

Author Contribution:

Dr. Salma Shaikh: Conception and design, analysis and interpretation of data.
Dr. Shazia Memon: Final revision of manuscript.
Dr. Hafeezullah Memon and Dr. Imran Ahmed: Collected and interpreted the data in out-patient department.