Tropical Medicine and International Health doi:10.1111/j.1365-3156.2009.02246.x

VOLUME 14 NO 4 PP 1–8 APRIL 2009

Rapid malaria diagnostic tests *vs.* clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomized trial

Zeno Bisoffi[1,5], Bienvenu Sodiomon Sirima[2], Andrea Angheben[1], Claudia Lodesani[3], Federico Gobbi[1], Halidou Tinto[4] and Jef Van den Ende[6]

1 *Centre for Tropical Diseases, Sacro Cuore Hospital, Negrar (Verona), Italy*
2 *Centre National de Recherche et de Formation sur le Paludisme, Ministry of Health, Ouagadougou, Burkina Faso*
3 *Medecins sans Frontières, Democratic Republic of Congo*
4 *Centre Muraz, Bobo Dioulasso, Burkina Faso*
5 *Projet AnKaHeresso, Bobo Dioulasso, Burkina Faso*
6 *Department of Clinical Sciences, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium*

Summary

OBJECTIVES To assess if the clinical outcome of patients treated after performing a Rapid Diagnostic Test for malaria (RDT) is at least equivalent to that of controls (treated presumptively without test) and to determine the impact of the introduction of a malaria RDT on clinical decisions.

METHODS Randomized, multi-centre, open clinical trial in two arms in 2006 at the end of the dry and of the rainy season in 10 peripheral health centres in Burkina Faso: one arm with use of RDT before treatment decision, one arm managed clinically. Primary endpoint: persistence of fever at day 4. Secondary endpoints: frequency of malaria treatment and of antibiotic treatment.

RESULTS A total of 852 febrile patients were recruited in the dry season and 1317 febrile patients in the rainy season, and randomized either to be submitted to RDT (P_RTD) or to be managed presumptively (P_CLIN). In both seasons, no significant difference was found between the two randomized groups in the frequency of antimalarial treatment, nor of antibiotic prescription. In the dry season, 80.8% and 79.8% of patients with a negative RDT were nevertheless diagnosed and treated for malaria, and so were 85.0% and 82.6% negative patients in the rainy season. In the rainy season only, both diagnosis and treatment of other conditions were significantly less frequent in RDT positive *vs.* negative patients (48.3% *vs.* 61.4% and 46.2% *vs.* 59.9%, $P = 0.00$ and 0.00, respectively).

CONCLUSION Our study was inconclusive on RDT safety (clinical outcome in the two randomized groups), because of an exceedingly and unexpectedly low compliance with the negative test result. Further research is needed on best strategies to promote adherence and on the safety of a test based strategy compared with the current, presumptive treatment strategy.

keywords malaria management, malaria diagnosis, fever management, rapid diagnostic test, RDT safety, clinical decision

Introduction

In recent years, following WHO recommendations, most African countries have adopted treatment protocols for malaria based on artemisinin combination treatments (ACT) (Ogbonna & Uneke 2008). The new protocols have proven to be very effective, but they are also much more expensive than previous regimens. The presumptive treatment of all fevers for malaria, previously a current practice, has therefore being questioned on economical grounds (Pfeiffer *et al.* 2008). Moreover, presumptive treatment is considered potentially dangerous as it might contribute to selecting for resistant *Plasmodium falciparum* strains. New guidelines for malaria management recommend a mandatory laboratory test before malaria treatment (WHO 2006). In many African areas without laboratory facilities, the only possibility is the use of a rapid diagnostic test (RDT).

Paracheck® (Orchid Biomedical Systems, Goa, India) is the most widely used RDT. It is based on the detection of the *P. falciparum* specific HRP-2 protein and diagnoses malaria infection rapidly and with reasonable accuracy according to most studies, with 90.1–100% sensitivity and 52–99.5% specificity (Guthmann *et al.* 2002; Singh &

Saxena 2005; Singh *et al.* 2005; van den Broek *et al.* 2006; Swarthout *et al.* 2007; Murray *et al.* 2008).

In Burkina Faso the adoption of the new ACT based strategy is very recent, and in 2006 had yet to be implemented. In a context of a highly variable, seasonal transmission, the safety and utility of the introduction of a RDT for malaria was discussed. We decided therefore to study the safety, utility and cost-effectiveness of a RDT based strategy *vs.* the current, presumptive clinical management in a region where malaria incidence is highest, and where no laboratory facility is available at periphery. We also wanted to assess how the prescribing behaviour of health personnel (nurses) was affected by the availability of the new test, and in particular, the adherence to a negative test result. Safety and adherence are the object of the present paper. The safety did not concern RDT testing in itself, but rather the subsequent prescribing; theoretically, harm could be caused both by a false negative and a false positive result (Bisoffi & Van den Ende 2008): False negatives would not be treated for malaria; false positives would risk to be left without treatment for the true cause of their fever. We aimed to assess if the new strategy would be at least equivalent to the previous (presumptive) one in terms of short term clinical outcome. The issue of adherence to malaria diagnosis has recently been investigated (Reyburn *et al.* 2004, 2007; Hamer *et al.* 2007), but most of these studies were not yet published at the time of our field study (2006). The cost effectiveness of RDT based strategies has been questioned due to lower-than-expected compliance of health workers with the (negative) test result (Bisoffi & Van den Ende 2008; Lubell *et al.* 2008).

We hypothesized that (i) the short-term health outcome should not be worse in the group submitted to RDT; (ii) less frequent malaria treatment, and more frequent treatment for other causes of fever, mainly antibiotics, should be observed in febrile patients with a negative RTD result; (iii) the opposite should be observed in febrile patients with a positive RTD result. Thus our objectives were: to assess if the short-term outcome (day 4) of patients treated after performing a RDT is at least equivalent (not inferior) to that of controls (without RDT) in terms of clearance of fever and of other major symptoms and signs; and to assess the impact of the introduction of a malaria rapid diagnostic tests (RDT) on clinical decisions by health officers.

Patients and methods

Type of study

This was a randomized, multi-centre, open clinical trial (RCT) in two arms: one arm with use of RDT before treatment decision (cases or P_RTD), the other managed clinically according to national guidelines (controls or P_CLIN). The primary endpoint was the persistence of fever at day 4. Secondary endpoints were persistence of other main clinical findings at day 4, frequency of malaria treatment in both randomized groups and according to RDT result, frequency of antibiotic treatment in both randomized groups and according to RDT result.

Patients

The study took place in 10 peripheral health centres of the provinces of Bobo Dioulasso and Banfora, south-west Burkina Faso, an area with stable malaria and with a seasonal transmission pattern. The health centres were selected according to convenience criteria such as: number of malaria cases reported in previous years; geographical (and urban/rural) representativeness; sufficient number of health professionals able to carry out the study. Half of the centres were supported by the health project An Ka Heresso, financed by the Italian Foundation UNIDEA and carried out by an Italian NGO, while the others were public health facilities with no special external support.

Inclusion criteria were: age ≥6 months and presenting at the health centre with an axillary temperature ≥37.5 °C. Exclusion criteria were severe clinical condition requiring urgent action. All patients attending the health centres were initially assessed by ordinary dispensary staff (in the study area all were nurses) who decided on eligibility for inclusion. Eligible patients were given (by research assistants) a detailed explanation of the study and asked for informed consent. Patients included in the study were assigned to either arm based on the randomization list (see below). Research assistants directly assisted at the following consultation carried out by the nurse, filled in a standardized questionnaire reporting main clinical findings, the working and final diagnosis and all treatments administered, and performed the RDT (for P_RDT) and a thick and thin film (for all), to be stored for subsequent reading.

Sample size

The sample size was determined for the primary endpoint, that is, fever persistence at follow-up (day 4). This was used as a surrogate for severe outcomes that were expected to be very rare and would have needed a sample size not attainable by this study. For an expected frequency of fever persistence at day 4 in subjects managed clinically (P_CLIN) of 40% and a maximal expected difference of 10% (for a power of the study of 80% and an alpha error of 5%), a sample size of 814 in

each season would be needed. We planned to enrol at least 500 subjects per arm in both seasons, in order to account for loss to follow up.

Randomization

Febrile patients included in the trial were assigned to either arm based on a computer-generated random list. In each study period of 1 month at the end of the dry and rainy season, all patients included were randomized to be submitted to RDT (Paracheck® test) (cases or P_RTD), or to be managed clinically (controls or P_CLIN).

Clinical management and follow-up

Clinical findings were recorded for all patients. In case of death the circumstances were investigated in depth and additional data were recorded in a separate notebook. The dispensary staff (nurses) remained responsible for the final diagnosis and treatment. Research assistants communicated (and showed) the test result of P_RDT to the nurses, but they were not authorized to question their decisions. A follow-up was carried out for all patients at day 4, when patients where examined again: those who failed to attend the clinic at day 4 were visited at home the same day or at latest the following day by research assistants.

Training

Research assistants (most were recently graduated, still unemployed junior nurses) were specially recruited for the study. They were intensively trained for 3 days on the study protocol and on the correct execution and reading of the RDT. The dispensary nurses were also trained on RDT reading and RDT performances as reported by literature. Key messages were that a negative RDT result virtually excluded clinical malaria, while a positive result did not rule out other possible causes of fever. Only Paracheck® result should be used for decision of malaria treatment for *cases* (P_RDT). Treatment of *controls* (P_CLIN), and treatment of any other condition for both *cases* and *controls*, should solely depend on the judgment of the clinical officer, based on the national diagnostic guidelines. Before the second phase of the field study in the rainy season, a booster training for three more days was given to both the research assistants and the nurses.

Ethical clearance

The study protocol was approved by the 'Comité National d'Ethique' (National Ethical Committee) of Burkina Faso. Written informed consent was obtained through the use of an information sheet with detailed explanation of the purpose of the study and the procedures involved. Once the nurse had decided that a patient was eligible for inclusion, a member of the investigational staff gave the explanation in local language, in the presence of an independent witness. In case of agreement, the informed consent form was signed both by the patient (or one of the parents in case of minors) and by the witness. Illiterate participants signed by fingerprint.

Data management and statistical analysis

Data (all categorical) were double entered and analysed with Epi Info software (EpiInfo, CDC Atlanta, version 3.3.2). The association between variables was expressed by odds ratio (OR) and its 95% confidence limits. Uncorrected chi-square test and the corresponding p values were used for statistical inference. Fisher exact test was used for values <5.

Results

As shown in the flow charts (Figures 1 and 2), 2861 patients were assessed for potential inclusion in the study in the dry season and 3573 in the rainy season. One thousand nine hundred and ninety-five and 2237 respectively did not respond to the inclusion criteria for reasons outlined in the flow charts, but 866 and 1336 were eligible for inclusion, of whom 14 and 19, respectively, refused. The remaining 852 and 1317 patients were recruited and randomized either to the RDT (P_RTD) or presumptive management on clinical grounds only (P_CLIN).

Of 852 febrile patients recruited in the dry season, 404 were submitted to the RDT and 448 treated presumptively. Of 1317 recruited in the rainy season 654 had RDT and 663 presumptive treatment. Demographic and clinical characteristics were evenly distributed in the randomized groups (Table 1).

Clinical outcome

Follow-up at day 4 was possible for 813 of 852 patients in the dry season (95.4%) and 1282/1317 patients (97.3%) in the rainy season. In the dry season, four deaths (two infants aged 10 and 15 months, respectively, and two adults) were recorded in the P_RDT group *vs.* three deaths (all infants) in the P_CLIN group ($P = 0.71$), while in the rainy season one death was reported in each cohort (one infant submitted to RDT and one adult not submitted) ($P = 1$). Subsequent microscopy showed that in the dry season no fatality was due to malaria (in only one case was

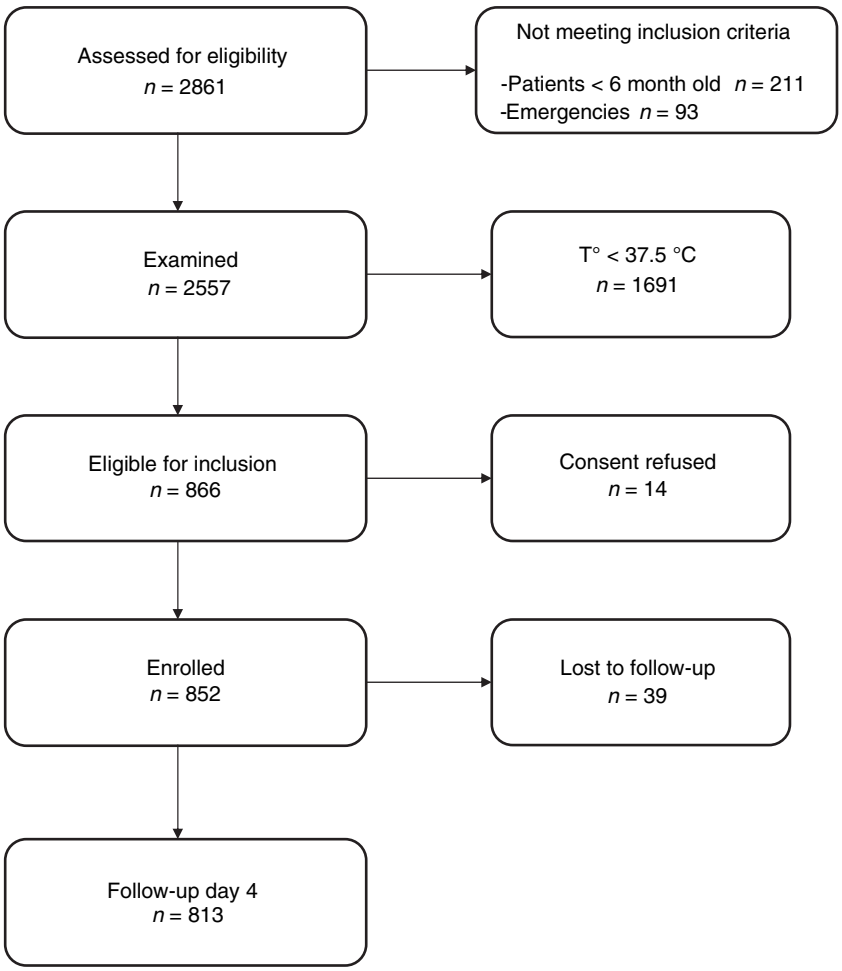

Figure 1 Trial profile, dry season.

the thick film positive, but at a very low parasitaemia of 120 parasites/μl). One of the infants had been treated for malaria only, after a positive RDT test, which was subsequently found to be a false positive. The infant who died in the rainy season had a malaria infection at very high parasitaemia (about 15%) and was appropriately treated after a positive RDT; the adult had no malaria parasite and presumably died of pneumonia.

The rates of persistence of fever (8.2% in both groups in the dry season, 3.9 *vs.* 3.7% in the rainy season) and of other symptoms (20.1 *vs.* 20.3% in the dry season, 6.4 *vs.* 8.5% in the rainy season) were also similar in both groups (Table 2).

Comparing the seasons as a whole, a significant worse outcome was found in the dry season (Table 3): lower rate of resolution of fever and of other symptoms (8.2% and 20.1% *vs.* 3.8% and 7.4%, respectively: $P = 0.00$ and 0.00), and higher death rate (7/813 or 0.9% *vs.* 2/1282 or 0.16%: $P = 0.03$).

Clinical decision

In the dry season, the rapid test result was positive in 113 of 404 (28%) patients and indeterminate in 4 (not considered in the analysis). In the rainy season, the RDT result was positive in 443 of 650 (68.2%) cases and indeterminate in four (not considered in the analysis). In both seasons, no significant difference was found between the two randomized groups in the frequency of final diagnosis of malaria (83.7% *vs.* 80.8% in dry season, $P = 0.28$, and 92.7% *vs.* 91.9% in rainy season, $P = 0.58$) and antimalarial treatment (84.2% *vs.* 80.1% in dry season, $P = 0.13$, and 92.5% *vs.* 92.0% in rainy season, $P = 0.73$) (Table 4).

In the dry season, an alternative diagnosis was made more often in P_CLIN than in P_RTD (73% *vs.* 64%, $P = 0.00$), but with no significant difference in antibiotic prescription (56.7% *vs.* 61.4%, $P = 0.16$). In the rainy season, both the frequency of other diagnoses and of

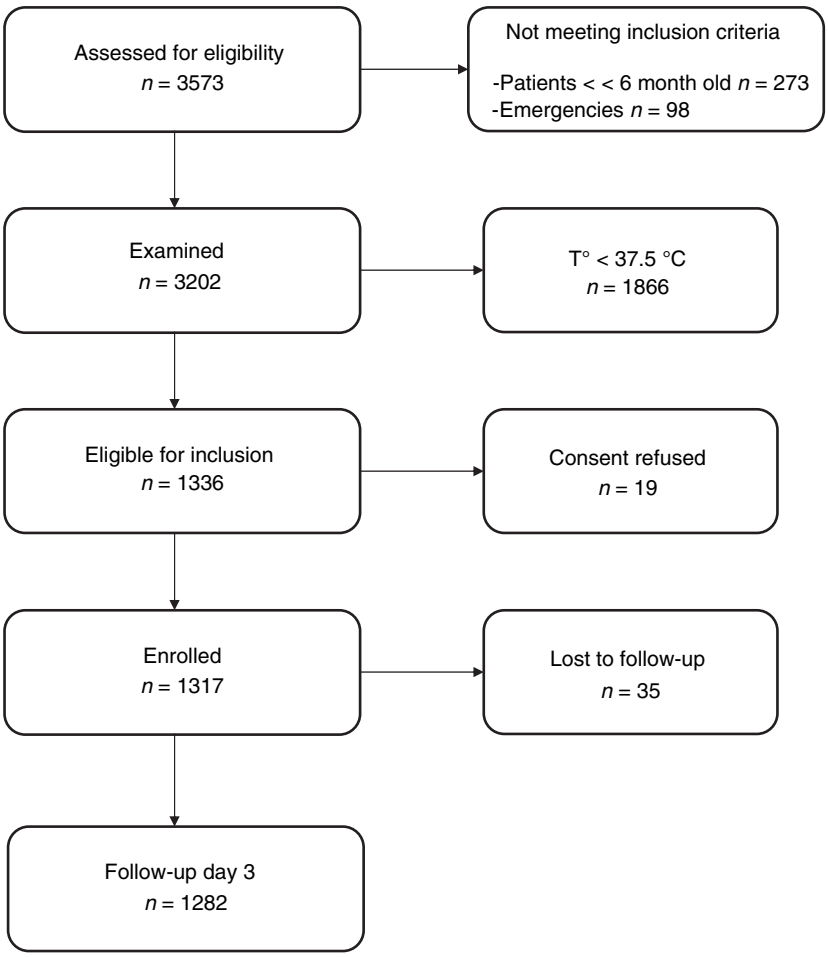

Figure 2 Trial profile, rainy season.

Table 1 Comparison of randomized groups

	RDT	Clinical	*P*
Sex			
M	517 (49.1%)	538 (48.6%)	0.96
F	527 (49.1%)	559 (50.5%)	
Age (years) (median)	4 Q1 = 1, Q2 = 19	4 Q1 = 1, Q2 = 18	0.98
T° (median)	38.3 Q1 = 37.8, Q2 = 39.1	38.3Q1 = 37.7, Q2 = 39	0.21
Vomiting	30.5%	29.9%	0.75
Diarrhoea	19.7%	20.7%	0.56
Cough	41.3%	41.2%	0.97
Skin rash	3.3%	2.7%	0.40
CNS alteration	1.3%	1.1%	0.46
ENT symptoms	3.8%	5.3%	0.08
Positive thick film	48.6%	46.2%	0.26

antibiotic prescriptions were similar in both groups (52.4% *vs.* 51.9%, $P = 0.83$, and 50.6% *vs.* 50.3%, $P = 0.93$, respectively) (Table 4).

Table 2 Clinical outcome at follow-up (day 4th) in the two arms

	RDT (%)	Clinical (%)	*p*
Dry season			
Death	4/388 (1.0)	3/425 (0.7)	0.71
Persistence of fever	32/388 (8.2)	35/425 (8.2)	0.99
Persistence of other symptoms	78/388 (20.1)	86/425 (20.2)	0.96
Rainy season			
Death	1/636 (0.15)	1/646 (0.15)	1
Persistence of fever	25/636 (3.9)	24/646 (3.7)	0.83
Persistence of other symptoms	41/636 (6.4)	55/646 (8.5)	0.16

A further analysis was carried out in the P_RDT arm only, in order to assess how decisions were influenced by the RDT result. As expected, in both seasons the frequency of malaria diagnosis and treatment was significantly higher for positive *vs.* negative RDT results (Table 5). In the dry season, 92% and 95.6% of patients with a positive RDT

Table 3 Clinical outcome at follow-up (day 4th) in the two seasons

	Dry season (%)	Rainy season (%)	*P*
Death	7/813 (0.9)	2/1282 (0.16)	0.03
Persistence of fever	67/813 (8.2)	49/1282 (3.8)	0.00
Persistence of other symptoms	164/813 (20.1)	96/1282 (7.4)	0.00

Table 4 Diagnosis and treatment of malaria and other conditions in the two arms

	RDT (%)	Clinical (%)	*P*
Dry season			
Diagnosis of malaria	338/404 (83.7)	362/448 (80.8)	0.28
Antimalarial treatment	340/404 (84.2)	359/448 (80.1)	0.13
Other diagnosis	257/404 (63.7)	328/448 (73.2)	0.00
Antibiotic treatment	229/404 (56.7)	275/448 (61.4)	0.16
Rainy season			
Diagnosis of malaria	606/654 (92.7)	609/663 (91.9)	0.58
Antimalarial treatment	605/654 (92.5)	610/663 (92.0)	0.73
Other diagnosis	343/654 (52.4)	344/663 (51.9)	0.83
Antibiotic treatment	331/654 (50.6)	334/663 (50.3)	0.93

Table 5 Malaria diagnosis and treatment according to RDT result

	Positive RDT (%)	*Negative RDT* (%)	*P*
Dry season			
Diagnosis of malaria	104/113 (92.0)	232/287 (80.8)	0.00
Antimalarial treatment	108/113 (95.6)	229/287 (79.8)	0.00
Other diagnosis	75/113 (66.4)	179/287 (62.5)	0.45
Antibiotic treatment	69/113 (61.0)	157/287 (54.7)	0.25
Rainy season			
Diagnosis of malaria	426/443 (96.2)	176/207 (85.0)	0.00
Antimalarial treatment	435/443 (98.2)	171/207 (82.6)	0.00
Other diagnosis	214/443 (48.3)	127/207 (61.4)	0.00
Antibiotic treatment	205/443 (46.2)	124/207 (59.9)	0.00

were diagnosed and treated for malaria, *vs.* 80.8% and 79.8% with a negative RDT ($P = 0.00$ and 0.00). In the rainy season, 96.2% and 98.2% of positive patients were diagnosed and treated for malaria, *vs.* 85.0% and 82.6% of negative patients ($P = 0.00$ and 0.00).

In the dry season the two arms did not differ significantly in the frequency of other diagnoses or antibiotic prescription (66.4% *vs.* 62.5% and 61.0% *vs.* 54.7%, $P = 0.45$ and 0.25, respectively) (Table 5). This was not the case in the rainy season, when the diagnosis and treatment of other conditions were less frequent in RDT positive patients (48.3% *vs.* 61.4% and 46.2% *vs.* 59.9%, $P = 0.00$ and 0.00, respectively) (Table 5). The additional training had no apparent effect on the diagnosis and treatment of malaria and of other conditions for RTD negative patients (Table 6).

Discussion

Despite a growing mass of literature on RDT for malaria, we were surprisingly unable to find any single paper on the safety of a RDT based strategy, compared with presumptive malaria management, and very few articles on adherence to RDT results (Hamer *et al.* 2007; Reyburn *et al.* 2007; Lubell *et al.* 2008). Test based strategies might fail their purpose to save unnecessary costs, and be even dangerous, if clear evidence on both aspects is not provided (Bisoffi & Van den Ende 2008; Lubell *et al.* 2008).

No significant difference was found in the clinical outcome between the two randomized groups (Table 2). Because of the poor adherence to the test result, we were not able to show if the RDT based strategy can be considered safe. Other authors found that malaria infections missed by microscopy and therefore untreated are not associated with mortality risk (Njama-Meya *et al.* 2007). Similar evidence for RDT is, however, still lacking.

Another potential harm affects RDT false positive patients. In endemic areas the presence of malaria parasites in blood may not reflect a clinical malaria episode (Schellenberg *et al.* 1994). Thus some febrile, RDT positive patients may be simple carriers of malaria parasites, with another (potentially severe) disease. The harm from a missed treatment, under the influence of a positive malaria test, might not be negligible. In one case in the dry season, a child with a false positive RDT result was treated for malaria only and subsequently died (presumably of pneumonia). The difference in mortality and clinical outcome between the two seasons (Table 3), as was recently found in Burkina Faso by other authors, raises concern (Kynast-Wolf *et al.* 2006). The difference might be due to a

Table 6 Effect of training: comparison between both seasons regarding diagnosis and treatment of malaria and other conditions

Diagnosis and treatment	Dry season (%)	Rainy season (%)	*P*
RDT negatives diagnosed as malaria	232/287 (80.8)	176/207 (85.0)	0.28
RDT negatives treated for malaria	229/287 (79.8)	171/207 (82.6)	0.50
Alternative diagnoses in RDT negatives	179/287 (62.5)	127/207 (61.4)	0.89
Antibiotic treatment in RDT negatives	157/287 (54.7)	124/207 (59.9)	0.29

different epidemiological pattern between the two seasons and/or to the fact that a patient was less likely to receive the appropriate treatment for her/his condition in the dry season when malaria is much less frequent.

No significant difference was found in either season between the two randomized groups for clinical decisions concerning malaria diagnosis and treatment. Other potential causes of fever were more frequently diagnosed in the dry season, though the frequency of antibiotic treatment was similar in the two arms (Table 4). In both seasons a positive RDT result was significantly correlated with the decision to treat for malaria (Table 5), but negative patients were also diagnosed as malaria cases in 80% (dry season) to 85% (rainy season) of cases. The expected, higher frequency of alternative diagnoses and treatments after a negative RDT result was only observed in the rainy season (after a second intensive 3-day training session) (Table 5). In general, more than half patients were treated with antibiotics, in both arms and in both seasons (Table 4), and so were about half patients with a positive RDT, despite being almost all diagnosed as malaria cases (Table 5). The so called 'double diagnosis' (and treatment) is questioned by Public Health officers as a waste of resources. In individual care, however, nurses often prefer to treat a potentially harmful cause of fever if they cannot rule it out.

Other authors have very recently addressed the adherence issue in African, Anglophone countries, (Hamer *et al.* 2007; Reyburn *et al.* 2007; Lubell *et al.* 2008) while we are not aware of any published study from Francophone Africa as yet. While the above referred studies have generally found a poor compliance with the negative test result, none has shown such a low adherence as in ours. Undoubtedly local concepts of illness influence malaria management (Beiersmann *et al.* 2007; Some & Zerbo 2007). Moreover, nurses were not compelled to refrain from malaria treatment in case of a negative result. This could be regarded as a major flaw in the study design. Also, ACT were not yet available in most health facilities: cheaper regimens (generally including amodiaquine), were used in most cases. Other authors have found in Kenya that clinical officers tend to reserve ACT for positive cases, and to treat negative patients with cheaper regimens (Zurovac *et al.* 2008).

During the second training session in the rainy season, it was particularly stressed that a negative test virtually excludes malaria. The result was frustrating. Even more negative patients were treated for malaria than in dry season (Table 6), probably reflecting the conviction that in the rainy season every febrile patient has malaria. Nurses intuitively feel that the pre-test probability of malaria is so high, that the disease remains likely even after a negative test.

This study has a major limitation. As we did not expect such poor adherence, the study failed to fulfil its first objective, that was, to assess a possible difference in clinical outcome between the two arms. One can argue that the study design was flawed, because in order to fulfil the main objective, adherence should have been enforced and strictly supervised. *A posteriori*, this is obviously true, but we planned to study the safety issue under near-real conditions, rather than in a quasi-experimental context that might not reflect everyday practice.

Some operational constraints must also be acknowledged. Not all clinical officers of the 10 health centres participating in the study were trained, due to logistic problems: while it was agreed that patients should be attended by trained nurses during the study period, this did not always prove possible. In some cases, the study supervisors found that the diagnosis and treatment decision were made before knowing the RDT result. Clearly, if this happened in the context of an intensively supervised study, we may expect it to occur even more in everyday practice. Finally, as the frequency of fever persistence at follow-up was lower than expected in both arms, the sample size would have been inadequate to the primary endpoint in any case.

Safety of a RDT-based strategy (especially for children below 5 years) remains a fundamental issue that should be addressed by future research. If safety is clearly demonstrated, policies to promote adherence will have a better evidence base (Bisoffi & Van den Ende 2008) Evidence in this respect should probably be pooled from different study settings in different countries. More research is also needed on adherence. Policy makers should seriously consider the issue of (non) adherence to diagnostic tests. Operational research should concentrate on effective strategies to promote compliance.

Conclusion

This study proves once more that the widespread introduction of RDT in malaria endemic countries is far from reaching the expected results. RDT for malaria can only be useful and cost effective if an acceptable compliance with the (negative) test result were achieved. Training and supervision should focus on clear, unambiguous guidelines to this purpose. The safety of RDT-based malaria management, especially for children, has not yet been proven, and requires further investigation.

Acknowledgements

We thank the patients who participated in the study, the personnel of the health centres involved and all the

investigation staff, as well as all the health staff of the 'An Ka Heresso' Project at the time of the field survey: Giuseppe Baracca (who first suggested a study on RDT), Klara Van den Ende, Annalisa Romeo, Bouma Neya, Mamadou Traore and Rosalie Midjour. We also thank Maria Gobbo, Monica Degani and Barbara Paiola for their active collaboration to the training of the investigational staff, Marleen Boelaert for support to data analysis and interpretation and Marco Albonico for critical reading of the manuscript. This study was funded by UNIDEA – UNICREDIT Foundation.

References

Beiersmann C, Sanou A, Wladarsch E *et al.* (2007) Malaria in rural Burkina Faso: local illness concepts, patterns of traditional treatment and influence on health-seeking behaviour. *Malaria Journal* **6**, 106.

Bisoffi Z & Van den Ende J (2008) Costs of treating malaria according to test results. *British Medical Journal* **336**, 168–169.

van den Broek I, Hill O, Gordillo F *et al.* (2006) Evaluation of three rapid tests for diagnosis of *P. falciparum* and *P. vivax* malaria in Colombia. *American Journal of Tropical Medicine and Hygiene* **75**, 1209–1215.

Guthmann JP, Ruiz A, Priotto G *et al.* (2002) Validity, reliability and ease of use in the field of five rapid tests for the diagnosis of *Plasmodium falciparum* malaria in Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **96**, 254–257.

Hamer DH, Ndhlovu M, Zurovac D *et al.* (2007) Improved diagnostic testing and malaria treatment practices in Zambia. *Journal of American Medical Association* **297**, 2227–2231.

Kynast-Wolf G, Hammer GP, Muller O, Kouyate B & Becher H (2006) Season of death and birth predict patterns of mortality in Burkina Faso. *International Journal of Epidemiology* **35**, 427–435.

Lubell Y, Reyburn H, Mbakilwa H *et al.* (2008) The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis. *British Medical Journal* **336**, 202–205.

Murray CK, Gasser RA Jr, Magill AJ & Miller RS (2008) Update on rapid diagnostic testing for malaria. *Clinical Microbiology Review* **21**, 97–110.

Njama-Meya D, Clark TD, Nzarubara B *et al.* (2007) Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children. *Malaria Journal* **6**, 7.

Ogbonna A & Uneke CJ (2008) Artemisinin-based combination therapy for uncomplicated malaria in sub-Saharan Africa: the efficacy, safety, resistance and policy implementation since Abuja 2000. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **102**, 621–627.

Pfeiffer K, Some F, Müller O *et al.* (2008) Clinical diagnosis of malaria and the risk of chloroquine self-medication in rural health centres in Burkina Faso. *Tropical Medicine and International Health* **13**, 418–426.

Reyburn H, Mbatia R, Drakeley C *et al.* (2004) Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. *British Medical Journal* **329**, 1212.

Reyburn H, Mbakilwa H, Mwangi R *et al.* (2007) Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. *British Medical Journal* **334**, 403.

Schellenberg JR, Smith T, Alonso PL & Hayes RJ (1994) What is clinical malaria? Finding case definitions for field research in highly endemic areas. *ParasitologyToday* **10**, 439–442.

Singh N & Saxena A (2005) Usefulness of a rapid on-site *Plasmodium falciparum* diagnosis (Paracheck PF) in forest migrants and among the indigenous population at the site of their occupational activities in central India. *American Journal of Tropical Medicine and Hygiene* **72**, 26–29.

Singh N, Saxena A, Awadhia SB, Shrivastava R & Singh MP (2005) Evaluation of a rapid diagnostic test for assessing the burden of malaria at delivery in India. *American Journal of Tropical Medicine and Hygiene* **73**, 855–858.

Some DT & Zerbo R (2007) Atypical etiology of malaria: local perceptions and practices for treatment and prevention in the department of Gaoua, Burkina Faso. *Medicine Tropicology (Mars.)* **67**, 43–47.

Swarthout TD, Counihan H, Senga RK & van den Broek I (2007) Paracheck-Pf accuracy and recently treated *Plasmodium falciparum* infections: is there a risk of over-diagnosis? *Malaria Journal* **6**, 58.

WHO (2006) *WHO guidelines for treatment of malaria*. WHO, Geneva. WHO/HTM/MAL/2006.1108.

Zurovac D, Njogu J, Akhwale W *et al.* (2008) Effects of revised diagnostic recommendations on malaria treatment practices across age groups in Kenya. *Tropical Medicine and International Health* **13**, 784–787.

Corresponding Author Zeno Bisoffi, Centre for Tropical Diseases, Sacro Cuore Hospital, Negrar (Verona), Italy.
E-mail: zeno.bisoffi@sacrocuore.it