The Benefits or Otherwise of Managing Malaria Cases with or without Laboratory Diagnosis: The Experience in a District Hospital in Ghana

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Abstract

Background: This study was conducted at the Kintampo Municipal Hospital in Ghana to determine whether there was any benefit (or otherwise) in basing the management of cases of suspected malaria solely on laboratory confirmation (microscopy or by RDT) as compared with presumptive diagnosis.

Method: Children under five years who reported at the Out-Patient Department of the Hospital with axillary temperature ≥37.5°C or with a 48 hr history of fever were enrolled and had malaria microscopy and RDT performed. The attending clinician was blinded from laboratory results unless a request for these tests had been made earlier. Diagnosis of malaria was based on three main methods: presumptive or microscopy and/or RDT. Cost implication for adopting laboratory diagnosis or not was determined to inform malaria control programmes.

Results: In total, 936 children were enrolled in the study. Proportions of malaria diagnosed presumptively, by RDT and microscopy were 73.6% (689/936), 66.0% (618/936) and 43.2% (404/936) respectively. Over 50% (170/318) of the children who were RDT negative and 60% (321/532) who were microscopy negative were treated for malaria when presumptive diagnoses were used. Comparing the methods of diagnoses, the cost of malaria treatment could have been reduced by 24% and 46% in the RDT and microscopy groups respectively; the reduction was greater in the dry season (43% vs. 50%) compared with the wet season (20% vs. 45%) for the RDT and microscopy confirmed cases respectively.

Discussion/Conclusion: Over-diagnosis of malaria was prevalent in Kintampo during the period of the study. Though the use of RDT for diagnosis of malaria might have improved the quality of care for children, it appeared not to have a cost saving effect on the management of children with suspected malaria. Further research may be needed to confirm this.

Some studies have shown that more than 50% of patients who were microscopy negative for malaria were treated for the disease [10,11]. Presumptive treatment for malaria was common in the era of cheap drugs like chloroquine and sulphadoxine-pyrimethamine (SP). However with increased resistance to those drugs and the introduction of the much more expensive artesminin based combination therapy (ACT) [11,12,13], presumptive treatment of malaria has to be re-considered carefully [14,15,16,17].

The ease of operation and portability of malaria rapid diagnostic tests (RDTs) as compared with that of microscopy [17,18,19] make it possible for them to be deployed in remote areas as well as in primary health care settings. In 2009, a combination of RDT or microscopy with ACTs was found to potentially improve the diagnosis and management of malaria cases, reduce the wastage of anti-malarial drugs and prevent
resistance to antimalarials [11,20]. In settings with limited resources, evidence-based decision-making and prioritization is paramount. Restricting ACT to RDT/Microscopy positive cases alone could reduce the number of children with fever receiving ACTs by more than 50% [10,11]. This means that the costs incurred by programme managers on treatment could easily be halved.

There have been some opposing views on whether it is probably time for changes in current guidelines recommending that African children with fever should be managed presumptively for malaria. While English et al., (2009) have expressed reservations with any attempt to introduce policy changes seeking to change presumptive treatment of malaria in favour of laboratory confirmed diagnosis and treatment [21], D’Acremont et al. (2009) have stated that the presumptive management of fevers with antimalarials currently may no longer be safe [14].

With these varied opinions in mind, we investigated the benefit or otherwise in restricting the use of ACTs to cases of malaria diagnosed by RDT/Microscopy alone compared with those presumptively diagnosed for children less than five years of age reporting to the OPD of the Kintampo Municipal Hospital. We believe that the results from this study will contribute to narrowing the knowledge gaps in the advantages or otherwise of confirmatory diagnostics (microscopy and RDTs) in the management of malaria.

Methods

This was a cross-sectional study spanning the period from January 2009 to February 2010. It was an all-year round study that allowed for seasonality comparisons.

Study area

The study was conducted at the Kintampo Municipal Hospital in the Kintampo North Municipality of the Brong-Ahafo Region of Ghana, which has a resident population of about 75,000 people. The municipality is located within the forest-savannah transitional ecological zone of Ghana.

The rainy season in the study area occurs between April and November each year with an average rainfall of 1250 mm per annum and mean monthly temperatures between 18°C and 38°C. The area is holoendemic in terms of malaria transmission with a parasite prevalence of more than 50% among asymptomatic children less than 10 years of age [22]. The annual entomological inoculation rate is 269 infective bites per person per year. Malaria transmission occurs perennially and the major vectors are *Anopheles gambiae* and *Anopheles funestus* with slightly more than a quarter of children under five living in houses [22]. Studies carried out among children less than five years of age in the Kintampo area showed that children on the average could suffer up to seven (7) clinical episodes of malaria in a year [22].

Facilities for malaria microscopy are usually available at the hospital and the private clinics while RDTs are mainly used at the peripheral clinics. The community chemical shops are usually the first point of seeking medical care in the community and malaria diagnosis in the shops is mainly presumptive [23]. Currently, Artesunate-amodiaquine is the first line drug for the treatment of uncomplicated malaria in Ghana.

The municipal hospital is the referral point for the 13 Community-Based Health Planning and Service (CHPS) compounds, three [3] health centres at the sub-district levels and four private clinics in the municipality.

Table 1. Baseline demographic characteristics study participants.

| (N = 936) Categories | Age (months) |  |  |  |  |
|----------------------|--------------|----------|----------|----------|
|                      | 0−11         | 12−23    | 24−59    | Total    |
| n (%)                | n (%)        | n (%)    | n (%)    | n (%)    |
| **Sex**              |              |          |          |          |
| Males                | 132 (57.1)   | 131(50)  | 230(31.9)| 493(52.7) |
| Females              | 99 (42.9)    | 131(50)  | 230(48.1)| 443(47.3) |
| **Total**            | 231 (24.7)   | 262 (28) | 443 (47.3)| 936(100) |
| **Weight(kg): mean (SD)** |          |          |          |          |
|                      | 7.5(1.6)     | 9.6(1.5) | 12.7(2.4)| 10.6(3.0) |
| **Height-for-age z-score** | Mean ± SD (95% CI) |          |          |          |
|                      | −0.28±1.31 (−0.45,−0.11) |  | 0.08±1.26 (0.28,1.00) |  |  | −0.98±1.24 (−1.03,−0.42) |  | 0.75±1.30 (−0.83,−0.67) |  |  |
|                      | 0.64±2.36 (0.28,1.00) | 0.58±2.17 (0.88,−0.27) | 1.01±1.41 (−1.16,−0.86) |  | 0.50±1.99 (−0.65,−0.36) |  |  |
|                      | −0.73±1.99 (−1.03,−0.42) | −0.74±1.70 (−0.98,−0.51) | −0.63±1.60 (−0.80,−0.46) |  | 0.69±1.73 (−0.81,−0.56) |  |  |
| **MUAC*(cm) (n = 920) Mean (SD)** |  |  |  |  |
|                      | 14.1(1.4)    | 14.3(1.2) | 15.1(1.3) | 14.7(1.4) |

*MUAC- Mid Upper Arm Circumference.*
within the previous 48 hours. Children five years of age and above and any child admitted to the hospital with severe disease were excluded from the study.

Project staff who were stationed at the OPD identified potential study participants who were children already seen and managed by a clinician. A finger-prick blood sample (approximately 1 ml) was taken from the child by a trained laboratory technician using sterile procedures for preparation of a blood smear for microscopy examination and an RDT to confirm the presumptive diagnosis made by the clinician. The smears were independently read by two microscopists who were blinded to the results of the RDT as well as the diagnosis (es) made by the clinicians. If there was any discordance between the results of the two readers, a third and most experienced microscopist read the slide the third time, the agreement between the third reader and any of the earlier two was accepted as the final. Any asexual Plasmodium falciparum parasites identified were counted against 200 white blood cells. A smear was declared negative if no parasites were found after examining 100 high power fields. The parasite density was determined from the positive smears. Laboratory results from any of the tests mentioned above were made available to the clinician only upon request. No attempt was made by the study to change the treatment practices at the hospital at that time (which in most cases was presumptive). At the time of the study children were treated according to the national IMCI guidelines which included presumptive treatment with artesunate amodiaquine and followed up. However, if a child came back unwell, the laboratory results including the blood slide results were made available to the clinician.

Data management
All study forms were checked by the study coordinator for completeness and consistency prior to submission for data entry. Data was double entered independently into Microsoft Access database and verified. Consistency and range checks were also done and problems identified were resolved.

Statistical analyses
The cleaned dataset was analyzed using appropriate tests in Stata 11.0. Socio-demographic characteristics of study participants that were categorical variables were summarized into proportions, while quantitative variables such as MUAC were summarized into means together with their standard deviations. The level of agreement between microscopy and RDT was estimated using the Kappa Statistic.

Cost of treatment relative to diagnostic methods. The study also sought to determine any differences in the cost of malaria treatment based solely on presumptive diagnosis or by laboratory confirmation. Various cost scenarios were evaluated: one was the total cost of anti-malarial treatment prescribed for subjects for whom a presumptive diagnosis of malaria had been made. This cost covered only the costs of ACTs prescribed and did not include the cost of services provided. Similar costs were calculated for subjects who were diagnosed as positive for malaria by the other two methods of diagnosis – the “Cost of malaria treatment”. Another cost was calculated separately for each group of subjects who had a positive diagnosis of malaria by either of the two laboratory diagnostic methods. This was done for each child in each group by adding the cost of antimalarials prescribed for that child to the cost of the diagnostic method – $1.00 for each RDT and $2.50 for each microscopy done (termed “Total cost of malaria treatment”). The unit cost of malaria microscopy used in the analysis was based on the cost of malaria microscopy under the Mutual Health Insurance Scheme in Ghana at the time of the study. In the second cost scenario, the two types of cost were each calculated per subject for the three diagnostic methods. Both cost scenarios were assessed separately for the wet and dry seasons. The cost of antibiotics was not included in the data analysis.

Table 2. Clinical features of respondents (symptoms at presentation).

| Symptoms          | n (% ) |
|-------------------|--------|
| Poor Appetite     | 555 (59.5) |
| Cough             | 464 (49.8) |
| Vomiting          | 429 (46.0) |
| Diarrhoea         | 298 (32.0) |
| Irritability      | 39 (4.2)   |
| Fast breathing    | 18 (1.9)   |
| Difficulty in breathing | 6 (0.6)   |

doi:10.1371/journal.pone.0058107.t002

Figure 1. Over-diagnosis and missed diagnosis of Malaria.
doi:10.1371/journal.pone.0058107.g001
Ethical considerations. The study received ethical clearance from the institutional ethics committee of the Kintampo Health Research Centre (KHRC), Ghana Health Service (GHS). Mothers/caretakers voluntarily signed or thumb-printed an informed consent form after the study was fully explained to them before their children were enrolled in the study. Data was stored in locked cabinets to ensure participant confidentiality, and was only accessible to investigators and permitted members of the study team. Participants were only identified with a unique study code.

Results
Baseline characteristics
Nine hundred and forty (940) caregivers were contacted to participate in the study out of which 936 (99.6%) consented to participate and their children were enrolled into the study. All these children had both microscopy and RDT results for comparison with the study clinicians’ diagnoses and were used for the data analysis. Table 1 shows the general characteristics of the children in the study.

Children recruited into the study were between 1 month and 59 months of age (mean = 24 months) with 52.7% of them being males. Children between the ages of 24 months and 59 months constituted the largest proportion of study participants. There was not much difference between the proportions of children in the 0–11 month and 12–23 month age groups (24.7% vs. 28.0%). The Z-scores were based on the WHO 2005 Standard population.

Table 2 shows the various symptoms that the children presented with at the hospital. The most prevalent symptoms on presentation were poor appetite, cough, vomiting and diarrhea. Axillary temperatures recorded ranged between 35.7°C and 40.7°C (mean = 37.6°C).
Characterization of diagnosis based on presumption, microscopy or RDT

The proportions of malaria which were diagnosed presumptively, by RDT and by microscopy were 73.6% (689/936), 66.0% (618/936) and 43.2% (404/936) respectively. Figure 1 shows the proportions of presumptively treated malaria cases which were diagnosed as having the disease by the two confirmatory methods. Microscopy revealed that just a little over half (53.6%) of the children who were presumptively diagnosed with malaria and were treated with ACTs, were positive for the disease. With RDT, 75.5% of the same patients had malaria. Microscopy and RDT identified 14.2% and 39.7% respectively of the children as being positive for malaria even though they were presumptively diagnosed as non-malaria cases and therefore not treated with ACTs.

The data was disaggregated by seasonality (Figure 2). Of the 936 children enrolled into the study, 82.8% and 17.2% were enrolled in the wet and dry seasons respectively. About three quarters of children were presumptively diagnosed with malaria in the wet season. Almost eighty percent (80%) of the presumptively diagnosed malaria cases in the wet season were positively confirmed as such by RDT in contrast to microscopy that confirmed just a little over half of them. In the dry season, microscopy and RDT confirmed almost similar proportions of the presumptively diagnosed malaria cases.

Table 3. Comparison between the laboratory diagnostic methods by seasons.

|                | Microscopy        |                |
|----------------|-------------------|----------------|
|                | Positive n (%)    | Negative n (%) |
| **Wet Season** |                   |                |
| RDT Positive   | 337 (43.5)        | 211 (27.2)     |
| RDT Negative   | 6 (0.8)           | 221 (28.5)     |
| **Dry Season** | 58 (36.0)         | 12 (7.5)       |
| RDT Positive   | 3 (1.9)           | 88 (54.7)      |
| **Overall**    | 395 (42.2)        | 223 (23.8)     |
| RDT Positive   | 9 (1.0)           | 309 (33.0)     |

Sensitivity and specificity of Presumptive diagnosis and RDT

Table 4. Sensitivity and Specificity of Presumptive diagnosis and RDT diagnosis of malaria by seasons using Microscopy as the gold standard (with 95% CI).

|                | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) |
|----------------|--------------------------|--------------------------|------------------|------------------|
| **Presumptive vs. Microscopy** |                     |                          |                  |                  |
| **WET**        | 93.3 (90.1–95.7)         | 39.8 (35.2–44.6)         | 55.2 (51.0–59.3) | 88.2 (82.8–92.4) |
| **DRY**        | 80.3 (68.2–89.4)         | 39.0 (29.4–49.3)         | 44.6 (35.1–54.3) | 76.5 (62.5–87.2) |
| **OVERALL**    | 91.3 (88.2–93.4)         | 39.7 (35.5–44.0)         | 53.5 (49.7–57.3) | 85.8 (80.8–89.9) |
| **RDT vs. Microscopy** |                     |                          |                  |                  |
| **WET**        | 98.3 (96.2–99.4)         | 51.2 (46.3–56.0)         | 61.5 (57.3–65.6) | 97.4 (94.3–99.0) |
| **DRY**        | 95.1 (86.3–99.0)         | 88.0 (80.0–93.6)         | 82.9 (72.0–90.8) | 96.7 (90.7–99.3) |
| **OVERALL**    | 97.8 (95.8–99.0)         | 58.1 (53.8–62.3)         | 63.9 (60.0–67.7) | 97.2 (94.7–98.7) |

Only one percent (1%) of children diagnosed as non-malaria cases by RDT in the dry season was identified as positive for the disease by microscopy. Almost a quarter (23.8%) of study subjects diagnosed as malaria cases by RDT were not confirmed by microscopy (Table 3).

Sensitivity and specificity of Presumptive diagnosis and RDT

The sensitivity of the presumptive method in diagnosing malaria in the wet and dry seasons was 93.3% and 80.3% respectively (Table 4). The RDT showed both a higher sensitivity and specificity for diagnosing malaria as compared to presumptive diagnosis though both methods were not highly specific in diagnosing the disease. The sensitivities of both presumptive and RDT in diagnosing malaria decreased in the dry season with the decrease for the presumptive method (from 93.3% to 80.3%) greater than that for the RDT (98.3% to 95.1%). While there was virtually no decrease in the specificity of the presumptive method in diagnosing malaria between the two seasons, that of the RDT rather increased in the dry season (from 51.2% to 88.0%). Overall, using microscopy as the gold standard, the sensitivity and specificity of the RDT used were 97.8% (95% CI 95.8–99.0) and 58.1% (95% CI 53.8–62.3) respectively. Children who were presumptively diagnosed as non-malaria cases had a lower mean parasite density [5613 (95% CI 2645, 11 915)] compared to children presumptively diagnosed as malaria cases [38 310 (95% CI 31 270, 46 936)].
cost of treatment, RDT and microscopy were more expensive than presumptive treatment (Table 6). The cost of malaria treatment per subject was the same for all three methods except for a very marginal difference in the dry season. However, the total cost of treatment was 2.3 and 4.2 times more for the RDT and microscopy respectively as compared to the presumptive method (Table 6).

### Discussion

This study showed that the highest frequency of treatment for malaria (73.6%) was recorded by the presumptive method of diagnosis followed by RDT (66%) and microscopy (43.2%). Results from this study are similar to those in Tanzania which showed that over 50% of patients for whom antimalarials were prescribed may not have had the disease [2,3]. As shown in Figure 1, close to half of the children who were presumptively prescribed may not have had the disease [2,3]. As shown in Figure 1, close to half of the children who were presumptively treated for malaria were microscopy negative. Over-diagnosis of malaria and consequent treatment is a public health problem because it leads to increased reporting of the malaria burden with resultant misallocation of resources to manage the disease, wastage of antimalarials and increased threat of resistance to ACTs. It also results in increased attendance to health facilities due to poor response to treatment (potential misdiagnosis of serious non-malarial infections) and consequent increased workload on the already under-staffed and inadequately resourced health facilities [6,10]. With major concerns about parasite resistance development to the ACTs and the high costs of the ACTs, the judicious use of these drugs needs to be given high priority.

The high levels of agreement recorded between RDT and microscopy as diagnostic methods means in transmission areas comparable to ours, one of these diagnostics methods if available, is sufficient as a diagnostic method for malaria. The World Health Organization (WHO) recommends laboratory confirmation (either by microscopy or RDT) of all suspected malaria cases before treatment is commenced and that presumptive treatment should only be considered where such confirmation cannot be done [1]. Of the two laboratory methods, RDTs appear to be the method receiving the more prominent attention as they are perceived as having the potential to make a significant impact on improving the diagnosis of malaria. This is because RDTs produce quicker results; do not require any high level of skills to perform them, as opposed to microscopy, which requires more time and reagents, equipment and well-trained/dedicated staff to produce quality results [6,10,25].

In this study, the RDT had a high sensitivity (97.7%) but a rather low specificity (58.1%) for detecting malaria. In terms of diagnosing malaria there was moderate agreement between RDT and microscopy (Kappa = 0.53) [4]. The Parascreen® RDT used in this study satisfies one of the criteria for a useful diagnostic tool for RDTs with its high sensitivity (97.7%) but not for specificity. In spite of its low overall specificity, the marked increase in its specificity from 51.2% in the rainy season to 88.0% in the dry season showed that it could be a valuable tool to use to improve the diagnosis of malaria during the dry period, especially as there was not much decrease in its sensitivity during the same period. This means that the specificity of the RDT is critical in the dry season when the prevalence of malaria is relatively lower. On the other hand, a high sensitivity of the RDT will be required in the wet season when the malaria prevalence is very high.

As earlier stated, almost a quarter of study subjects diagnosed as malaria cases by RDT were not confirmed by microscopy (Table 3). This was likely due to prior treatment with antimalarials

### Table 5. Level of agreement between various malaria diagnostic methods.

| Method of Diagnosis                  | % Agreement | Kappa statistic | p-value |
|--------------------------------------|-------------|----------------|---------|
| Microscopy and Presumptive malaria   | 62.1        | 0.29           | P < 0.001|
| RDT and Presumptive malaria          | 71.5        | 0.33           | P < 0.001|
| Microscopy and RDT                   | 75.2        | 0.53           | P < 0.001|

Table 5. Level of agreement between various malaria diagnostic methods.

| Method of diagnosis                  | Total Cost for all subjects | Per patient cost |
|--------------------------------------|----------------------------|------------------|
|                                       | Cost of malaria treatment  | Cost of malaria  |
|                                       | in USD (95% CI)             | treatment in USD** (95% CI) | treatment in USD (95% CI) | treatment in USD** (95% CI) |
| **Total malaria treatment costs.**    |                            |                  |
| WET SEASON                            |                            |                  |
| Presumptive (N = 580)                 | 452.29 (429.27–475.32)     | 0.78 (0.74–0.82) |
| RDT (N = 463)                         | 363.30 (341.88–384.72)     | 0.78 (0.74–0.83) |
| Microscopy (N = 320)                  | 249.48 (232.14–266.82)     | 0.78 (0.73–0.83) |
| DRY SEASON                            |                            |                  |
| Presumptive (N = 109)                 | 75.84 (74.46–77.22)        | 0.70 (0.68–0.71) |
| RDT (N = 57)                          | 39.25 (37.95–40.55)        | 0.69 (0.67–0.71) |
| Microscopy (N = 49)                   | 33.65 (32.34–34.96)        | 0.69 (0.66–0.71) |
| OVERALL                               |                            |                  |
| Presumptive (N = 689)                 | 528.13 (505.03–551.24)     | 0.77 (0.73–0.80) |
| RDT (N = 520)                         | 402.55 (381.06–424.04)     | 0.77 (0.73–0.82) |
| Microscopy (N = 369)                  | 283.13 (265.72–300.55)     | 0.77 (0.72–0.81) |

**Cost of anti-malarial treatment+cost of diagnostic method.**

Cost of diagnostic method.

Table 6. Total malaria treatment costs.
with consequent clearing of parasitaemia and persistence of HRP2 antigenemia [26].

With regards to the cost of treatment in the various groups, overall the cost of treatment (per subject) (Table 6) did not differ among the three groups. The total cost of treatment was higher in the RDT and microscopy group even though fewer subjects were diagnosed with malaria in those groups than in the presumptive group. These results seem to suggest that RDTs are not cost-saving when used in the management of malaria in children less than five years, a result that is similar to that of Msellem et al. (2009), which found that cost-reduction using RDTs was not achieved among patients under 5 years but rather among those who were 15 years and above [27]. The low positive predictive value and specificity of the RDT lends possible credence to this negative cost-saving effect though the latter property of the RDT contrasts sharply with the 100% for both sensitivity and specificity recorded in a study by the manufacturer [24]. The cost of antibiotics was not included in this study. It is likely that children who had a false negative RDT were treated with antibiotics, however, this cost may not be lower than the cost of over-treatment of malaria with ACTs as suggested by Shillcott et al. [28].

Notwithstanding the high total cost of malaria treatment in the RDT group, a potential limiting factor for its use, the RDT can still be said to be an effective tool in reducing the over-diagnosis of malaria and the consequent use of ACTs in non-malaria cases, due to its high negative predictive value. The quality of care of such children will therefore be improved [14,15,17,29].

Limitations

One limitation of the study was that since it was a cross-sectional study, there was no follow up of the subjects. It therefore not possible to ascertain the clinical outcomes of the children who were presumptively treated for malaria (especially those for whom the diagnosis of malaria was not confirmed by RDT or microscopy) and those who were not treated for malaria even though they had been diagnosed as having the disease by the two laboratory methods.

Another possible limitation that since the study was conducted only in children less than five years of age and not in participants across all age groups, the possible cost-saving effect of the RDT could not be determined conclusively.

Acknowledgments

We are grateful to the parents and guardians who gave their consent for their children to be used in the study. We are also grateful to the Management and staff of the Kintampo Municipal Hospital for the use of the facility and also for providing other logistics support. We would also like to acknowledge the support of the project staff (Comfort Gyasi, Diata Adams, Patricia Owasu and Bright Nimako) in particular and staff of KHRC in general, towards the successful conduct of the study. We also thank Adams Mohammed, Kingpley Kayan, Gabriel Jakpa and Amirth Yakubu for helping with the laboratory aspect of the study and to the KHRC Scientific Review and Ethics Committees.

Author Contributions

Acceptance of manuscript for publication: KOK SA RO EM EK GA LA EY DKD DP KPA SOA. Conceived and designed the experiments: KOK SA LA KPA SOA RO. Performed the experiments: KOK RO SA EK DP. Analyzed the data: KOK EM KP SOA DKD GA. Contributed reagents/materials/analysis tools: DKD EM GA SOA KOK. Wrote the paper: KOK SA RO EM EK GA EY DKD DP KPA SOA.

References

1. WHO (2010) WORLD MALARIA REPORT.
2. Chandramohan D, Jaffar S, Greenwood B (2002) Use of clinical algorithms for diagnosing malaria. Trop Med Int Health 7: 45–52.
3. Nydromenyanji R, Magnusson P, Clarke S (2007) Diagnosis and treatment of malaria in peripheral health facilities in Uganda: findings from an area of low transmission in south-western Uganda. Malar J 6: 39.
4. Olivia M, Devleu M, Cheguo Abari A, Loutan I (1991) Presumptive diagnosis of malaria results in a significant risk of mistreatment of children in urban Sabah. Trans R Soc Trop Med Hyg 85: 729–730.
5. Rothe I, Bjorkman A (1992) Fever episodes in a holoendemic malaria area of Tanzania: parasitological and clinical findings and diagnostic aspects related to malaria. Trans R Soc Trop Med Hyg 86: 479–482.
6. Amexo M, Tollust R, Barnish G, Bates I (2004) Malaria misdiagnosis: effects of the poor and vulnerable. Lancet 364: 1896–1898.
7. Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF Macro (2009) Ghana Demographic and Health Survey 2008: Key Findings. Calverton, Maryland, USA: GSS, GHS, and ICF Macro. Available: http://www.measuredhs.com/pubs/pdf/SR172/ SR172.pdf. Accessed 2012 August 05.
8. Polage CR, Bedu-Addo G, Owasu-Ofori A, Frimpong E, Lloyd W, et al. (2006) Laboratory use in Ghana: physician perception and practice. Am J Trop Med Hyg 75: 326–331.
9. English M, Esamai F, Wasuna A, Were F, Ogutu B, et al. (2004) Assessment of inpatient paediatric care in first referral level hospitals in 13 districts in Kenya. Lancet 363: 1948–1953.
10. Reyburn H, Mbatia R, Drakeley C, Carnievo J, Mwakasungula E, et al. (2004) Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: a prospective study. BMJ 329: 1212.
11. Reyburn H, Mhakwana H, Mwangi R, Mweirde O, Olomi R, et al. (2007) Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. BMJ 334: 303–304.
12. Lubell Y, Reyburn H, Mhakwana H, Mwangi R, Chonya K, et al. (2007) The cost-effectiveness of parasitological diagnosis for malaria-suspected patients in an era of combination therapy. Am J Trop Med Hyg 77: 130–132.
13. Nankubwa J, Zurovac D, Ngpajj JN, Rwakirmaji JB, Cownahan H, et al. (2009) Malaria misdiagnosis in Uganda: implications for policy change. Malar J 8: 66.
14. D’Acremont V, Lengeler C, Mshinda H, Mtasiwa D, Tanner M, et al. (2009) Time to move from presumptive malaria treatment to laboratory-confirmed diagnosis and treatment in African children with fever. PLoS Med 6: e252.
15. Perkins MD, Bell DR (2000) Working without a blindfold: the critical role of diagnostics in malaria control. Malar J 7 Suppl 1: S3.
16. Murray CK, Bell D, Gasser RA, Wongrichanalai C (2003) Rapid diagnostic testing for malaria. Trop Med Int Health 8: 876–883.
17. Moody A (2002) Rapid diagnostic tests for malaria parasites. Clin Microbiol Rev 15: 66–78.
18. Bell D, Peeling RW (2006) Evaluation of rapid diagnostic tests: malaria. Nat Rev Microbiol 4: 334–38.
19. Wongrichanalai C (2001) Rapid diagnostic techniques for malaria control. Trends Parasitol 17: 307–309.
20. Webster J, Chandramohan D, Hanson K (2010) Methods for evaluating delivery systems for scaling-up malaria control intervention. BMC Health Serv Res 10 Suppl 1: S8.
21. English M, Reyburn H, Goodman C, Snow RW (2009) Abandoning presumptive antimalarial treatment for febrile children aged less than five years: a case of running before we can walk? PLoS Med 6: e1000015.
22. Owasu-Ofotu S, Asante KP, Adjiku M, Adjei G, Awini E, et al. (2009) Epidemiology of malaria in the forest-savanna transitional zone of Ghana. Malar J 8: 220.
23. Asante KP, Abokyi L, Zandoh C, Owasu R, Awini E, et al. (2010) Community perceptions of malaria and malaria treatment behaviour in a rural district of Ghana: implications for artemisinin combination therapy. BMC Public Health 10: 409.
24. Zephyr Biomedical Systems, Goa, India, /www.tulipgroup.com
25. Breman JG, Alilio MS, Mills A (2004) Conquering the intolerable burden of disease. Bull World Health Organ 86: 101–110.
26. Murray CK, Bennett JW (2009) Rapid Diagnosis of Malaria. Interdisip Percipt Infect Disv 9: 419–53.
27. Msellem MI, Martenson A, Rotllant G, Bhattachar G, Stromberg J, et al. (2009) Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanzibar: a crossover validation study. PLoS Med 6: e1000070.
28. Shillcutt S, Morel C, Goodman C, Coleman P, Bell D, et al. (2008) Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. Bull World Health Organ 86: 101–110.
29. Ishengoma DS, Franci F, Mbingo BP, Lusungu JP, Magistrado P, et al. (2011) Accuracy of malaria rapid diagnostic tests in community studies and their impact on treatment of malaria in an area with declining malaria burden in north-eastern Tanzania. Malar J 10: 176.