Comparative Rapid Diagnostic Test Kit and Presumptive Treatment of Fever Cases in the Hohoe Municipality, Ghana

Abstract

Background: Presumptive and test-based are the two main approaches for management and treatment of Malaria. The presumptive approach relies solely on clinical signs and symptoms to establish diagnosis while the test-based approach depends on laboratory investigation and confirmation. This study compared the use of rapid diagnostic test kit of fever to diagnose and manage Malaria during pre-rainy season (PRE-RS) and post-rainy season (POST-RS).

Methods: This was a cross-sectional comparative study in children less than five years carried out in June (PRE-RS) and November 2015 (POST-RS). The children were screened using Malaria rapid diagnostic test (RDT) during the PRE-RS and POST-RS respectively. Parents/guardians of the children were interviewed using a questionnaire. History of fever was determined if the parent/guardian admits the body of the child was hot within the past one week. The degree of association between RDT and history of fever was determined using Odds ratio (OR), and a measure of the degree of agreement between RDT usage and history of fever was determined using Kappa statistics. A p-value less than 0.05 was considered statistically significant.

Results: Overall, 1915 children were screened in the PRE-RS and 1697 in the POST-RS survey. In the PRE-RS survey, 217 children (11.3%) were positive for Malaria as determined by RDT while in the POST-RS survey 676 (39.8%) were positive. The history of fever within one week before the survey was 768 (40.1%) in PRE-RS and 966 (56.9%) in POST-RS survey. Using RDT was 2.18 times and 2.92 times more effective in detecting Malaria as compared to history of fever in PRE-RS and POST-RS (OR=2.18 (95% CI=1.64-2.90)) and (OR=2.92 (95% CI=2.37-3.59)) respectively. Agreement between RDT and history of fever usage was poor (kappa index=0.0912) during PRE-RS and slight (kappa index=0.2343) during POST-RS.

Conclusion: Using RDT to detect Malaria infection is more effective than relying on the history of fever. RDT use is also more effective in the POST-RS than PRE-RS. However, further studies are required to determine the cost effectiveness analysis of RDT use in both PRE-RS and POST-RS.

Keywords: Fever; Malaria infection; Rapid diagnostic test; Transmission; Seasons; Hohoe Municipality

Abbreviations: RDT: Rapid Diagnostic Test; PRE-RS: Pre-Rainy Season; POST-RS: Post-Rainy Season; OR: Odds Ratio; GHS-ERC: Ghana Health Service Ethical Review Committee; HRP2: Histidine Rich Protein 2; WHO: World Health Organization.

Introduction

The World Health Organization (WHO) Malaria report in 2015 indicated profound changes in the incidence of Malaria since the beginning of the millennium [1-22]. There were large reductions in the number of Malaria cases and deaths between 2000 and 2015. In 2000, it was estimated that there were 262 million cases of Malaria globally, leading to 839,000 deaths. By 2015, it was estimated that the number of Malaria cases had decreased to 214 million and the number of deaths to 438,000 [22]. These figures equate to an 18% decline in estimated Malaria cases and a 48% decline in the number of deaths during this period. Most cases in 2015 were estimated to occur in the African region (88%), followed by the South-East Asia region (10%) and the Eastern Mediterranean region (2%). Similarly, it was estimated that in 2015 most deaths (90%) were in the African region, followed by the South-East Asia region (7%) and the Eastern Mediterranean region (2%) [22]. The two main approaches to the diagnosis of Malaria are the presumptive and test-based approaches. The presumptive (or clinical judgment-based) approach relies solely on presenting signs and symptoms to establish diagnosis while the test-based approach relies on parasitological confirmation. For many years, the presumptive approach has been used across all age groups and transmission settings [23,24]. In early 2010, WHO issued revised guidelines for the management of Malaria that called for a shift from the presumptive to the test-based approach, across all transmission settings and in all age groups [23]. Over-diagnosis of Malaria implies inappropriate treatment of non-malarial febrile illness while a large proportion of such illnesses are self-limiting viral diseases, and a significant minority, are acute respiratory infections or bacterial diseases, which can be fatal. Diagnosis of Malaria based only on clinical grounds leads to significant overestimation of Malaria illnesses, even when diagnosis is carried out by experienced clinicians [18,19]. Misdiagnosis can expose patients to unnecessary side-effects of drugs and to the risk of overlooking potentially fatal conditions [17]. Fever cases in the past were equated with Malaria in many endemic countries and hence treated as such. It has however become clear that the continuous presumptive treatment of Malaria could lead to drug wastage hence the need for confirmation of cases by microscopy or rapid diagnostic test kits (RDT) prior to treatment [1]. It is therefore necessary to investigate further whether presumptive fever cases and RDT could be used as diagnostic tools to manage and treat Malaria. This study aimed at comparing results using RDT kit and presumptive treatment of fever cases in the Hohoe Municipality.

Materials and Methods

Study area

The study area is Hohoe Municipality, which is one of the twenty-five administrative districts of the Volta Region. The Municipality is located in the Volta region of Ghana with a population of 167,000 people. Just like most of Ghana, the Municipality has two main seasons, the wet and dry. The major wet season is from April to July and the minor one from September to November. The rest of the year is relatively dry. Malaria is hyper-endemic in the study area. Malaria transmission occurs throughout the year with seasonal peaks, coinciding with the period of the rains (high Malaria transmission begins from June and ends in November).

Study design

The study design was cross-sectional comparative. Data were collected in the form of interviews and biological samples obtained. The study population was all children in the selected Communities aged 6 to 59 months who were eligible and their parents/guardians consented to participate. Cross sectional surveys of children less than five years were carried out in June 2015 the beginning of the high transmission season, PRE-RS and at the end of the high transmission season, POST-RS in November 2015. The study involved asking parents/guardians questions on history of fever of the children within the past one week before the survey. Finger-prick blood sample was collected for determination of Malaria infection using RDT. The data obtained from RDT results in the two surveys was compared with reported fever cases.

Sampling and sample size calculation

Thirty Communities were selected from a sample frame of all Villages and Communities in the Municipality. The number of children living in each Community was determined from the 2000 census. Thirty Communities with the required number of children for the study (2,125) were randomly selected by probability, proportional to the number of children living in each Community. This sampling approach was used to ensure a fair representation of Communities in the Municipality in the study. The sample size was estimated on the basis of the following: 95% confidence level (Z) and power of 80%, the prevalence (P) of Malaria in children aged less than 5 years in June 2006 (end of dry season) was 8.6%. The least acceptable prevalence of Malaria was 5.0%. Using OpenEpi software version 3 (OpenEpi, 2013), the sample size calculated for each of the cross sectional studies was 1,648 children aged less than 5 years (Fleiss Statistical Methods with Continuity correction).

Laboratory Procedures

Rapid diagnostic testing of Malaria in human blood

CareStart™ Malaria HRP2 test kit (Access Bio Inc, New Jersey, USA) was used for the rapid qualitative detection of Malaria Histidine-rich protein 2 (HRP2) in human blood as an aid in the diagnosis of Malaria infection. Using this kit, 5 µL whole blood was introduced into the sample well by aid of pipette after finger pricking. Three drops of assay buffer was added to the buffer well. The result was read within 20 min.

Determination of history of fever

Parents/guardians were asked if they observed any fever in their children within the past one week before the survey. That is whether the child had hot body.

Statistical analyses

Data from participants were recorded on specified forms and
were checked by field supervisors and a data manager for consistency and accuracy. All data were entered twice into a database using EPI Data 3.1 software. The accuracy of data input was checked and validated using customized validation programmes. The cleaned data were converted to STATA version 12 (Stata Corporation, Texas, USA) file by a statistician prior to analysis. All analyses were done with STATA software version 12.0.

Cross tabulation was run to compare RDT and presumptive fever cases in the PRE-RS and POST-RS respectively. The odds ratio (OR) was used to explain relative measure of effect, which allowed the comparison of RDT in detecting Malaria relative to presumptive fever cases. Thus, OR=1 implies that there is no difference in RDT and presumptive fever cases in detecting Malaria. However, OR>1 implies that RDT is better or more effective than presumptive fever cases in detecting Malaria, whilst OR<1 means that RDT is less effective than presumptive fever cases. Kappa, which is a measure of concordance in categorical sorting or classification, was also used to measure the degree to which RDT and presumptive fever cases agree in their respective sorting or detection of Malaria. Different classifications have been developed for the interpretation of a given value of kappa. The classification used in this study was proposed [12]. Kappa values of 0.93 to 1.00 imply excellent agreement, 0.81 to 0.92: very good agreement, 0.61 to 0.80: good agreement, 0.41 to 0.60: fair agreement, 0.21 to 0.40: slight agreement, 0.01 to 0.20: poor agreement and -1.00 to 0.00: no agreement.

Results

Overall, 1915 children were screened in the first survey and 1697 in the second survey. In the PRE-RS survey 217 children (11.3%) were positive for RDT while in the POST-RS survey 676 (39.8%) were positive for Malaria with RDT. History of fever within one week before the survey was 768 (40.1%) in the PRE-RS and 966 (56.9%) in the POST-RS survey (Tables 1 and 2).

RDT was negative in 1698 (88.7%) and 1021 (60.2%) respondents during PRE-RS and POST-RS respectively. The PRE-RS indicates higher negativity for RDT. However, 1147 (59.9%) and 731 (43.1%) had no history of fever within one week in the PRE-RS and POST-RS respectively before recruited into the study. History of fever recorded was low during the POST-RS.

The Kappa values showed that there was no perfect agreement between using RDT and history of fever as diagnostic tools for Malaria management and treatment (Kappa=1). There was a slight agreement between RDT and presumptive fever with Kappa value of 0.2343 during the POST-RS whilst poor agreement was recorded during the PRE-RS (Kappa=0.0912). This suggests that RDT could be used preferably to diagnose Malaria before management and treatment during the POST-RS (Table 3).

Prevalence of history of fever was high (56.9%) in the POST-RS compared to 40.1% during the PRE-RS. The specificity (detection of true negative result) of the RDT usage during both seasons was high compared to the sensitivity (detection of true positive result). However, sensitivity and specificity patterns of the RDT used showed higher readings during the POST-RS compared to PRE-RS. The positive predictive values (PPV) recorded were 2.2% and 72.0% during the PRE-RS and POST-RS respectively. This depicts higher probability for using RDT to detect truly positive cases for Malaria during POST-RS. However, negative predictive values (NPV) recorded for the two seasons showed no significant difference. This explains use of RDT to detect true negative results for Malaria cases during both seasons were almost the same (PRE-RS=57% and POST-RS=53%). The Kappa index was slightly in agreement (0.2343) during the POST-RS compared to poor agreement (0.0912) in the PRE-RS (Table 3). This implies the agreement in using RDT to detect Malaria was better during the POST-RS compared to PRE-RS. Detection of Malaria by RDT was two times more effective than history of fever (OR=2.92, 95% CI=1.64-2.90) during the PRE-RS. Also, during the POST-RS, RDT was three times more effective than history of fever (OR=2.92, 95% CI=2.37-3.59).

Discussion

The prevalence of Malaria was high during the POST-RS compared to the PRE-RS. The study also recorded low specificity (74.1%) of RDT during the POST-RS, which is the high transmission season. This confirmed previous studies from Tanzania [9] and Ghana [1] with 63% and 73% specificities respectively. The high specificity (91.9%) in the low-transmission season was similar to another study in Uganda with 98.9% specificity using HRP2 antigen-based test [6]. In a Community with high frequency of Malaria infections together with long-lasting HRP2 antigens, quasi-persistent antigen positivity, results in children living in Communities with high Malaria transmission. This results into a recurrent Malaria infection before clearing the HRP2 antigens of the previous one. This may not be the case for children living in low-transmission settings, who are much less likely to have had a recent Malaria infection [6]. This could also be suggestive of the high prevalence of Malaria in the high transmission season and low in the low transmission season. Patient’s age, Malaria transmission intensity and lack of symptoms have been demonstrated to influence the specificity and sensitivity of RDTs, which can in turn result in under or over diagnosis of the disease [7,9,13,14]. The
The performance of different Malaria rapid diagnostic tests (RDTs) may be influenced by transmission intensity and by the length of time each test requires to become negative after treatment and patient’s recovery [11]. The length of time required in this study could not affect the results because the same RDT kit was used throughout the surveys.

It was demonstrated in a high-transmission setting in Ghana that the course of clinical recovery for RDT-negative children differed markedly from RDT-positive cases; overall treatment outcomes were comparable and no serious adverse effects were observed in children who were treated using the test-based approach [1]. Follow-up was not done in this study and therefore there was no record of any adverse effects. Also, comparator cohort was not used in this study. This was in accordance with previous studies that examined the effects of test-based management of Malaria and have been limited by the lack of appropriate comparator cohort [5].

Table 3: Performance characteristics of RDT with fever cases between two seasons.

<table>
<thead>
<tr>
<th>Validity Indicator</th>
<th>Pre-rainy season</th>
<th>Post-rainy season</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of RDT test done</td>
<td>1915</td>
<td>1697</td>
</tr>
<tr>
<td>Prevalence of history of fever (%)</td>
<td>40.1 (38.0, 42.3)</td>
<td>56.9 (55.0, 59.3)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>16.1 (13.6, 18.9)</td>
<td>50.4 (47.2, 53.6)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>91.9 (90.2, 93.4)</td>
<td>74.1 (70.8, 77.3)</td>
</tr>
<tr>
<td>Positive Predictive Value, PPV (%)</td>
<td>57.1 (50.3, 63.8)</td>
<td>72.0 (68.5, 75.4)</td>
</tr>
<tr>
<td>Negative Predictive Value, NPV (%)</td>
<td>62.1 (59.7, 64.4)</td>
<td>53.1 (50.0, 56.2)</td>
</tr>
<tr>
<td>Kappa Index</td>
<td>0.0912 (0.0583, 0.1241)</td>
<td>0.2343 (0.1894, 0.2792)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>2.18 (1.64, 2.90)</td>
<td>2.92 (2.37, 3.59)</td>
</tr>
</tbody>
</table>

The prevalence of Malaria parasitaemia is directly proportional to sensitivity and specificity of the RDT used. This implies that, sensitivity and specificity recorded are dependent on the prevalence rate of the disease condition in the population. Also, degrees of kappa correspond with the odds between RDT and fever usage as diagnostic tools during the seasons. The odds during the seasons were high, reporting use of RDT as preferable tool. This implies that we can use RDT for screening before treatment of Malaria cases. However, in early 2010, WHO issued revised guidelines for the management of Malaria that called for a shift from the presumptive to the test-based approach, across all transmission settings and in all age groups [21]. The current study is in accordance with the WHO guideline preferring test-based approach with RDT independent of the season of transmission.

Kappa values indicated that no perfect agreement exists between using RDT and history of fever as tools to diagnose Malaria (Kappa=1). There were slight and poor agreements during POST-RS (Kappa=0.2343) and PRE-RS (Kappa=0.0912) respectively. This submits that RDT and history of fever are diagnostic in 23% and 9% of the cases during both seasons. Nonetheless, more than 50% agreement (PA) was recorded using both RDT and fever as diagnostic tools. These agreements were in accordance with Viera and Garett classification [20]. However, Viera and Garret state limitations for kappa and these were also illustrated in a review [25]. They demonstrated that Kappa is affected by the prevalence of the finding under observation and the judgement of magnitude of Kappa is an open question. Therefore we chose odds ratio as an ideal statistical inference to interpret our observations with reference to the most effective diagnostic tool for Malaria detection. The two seasons recorded odds ratios >1. This shows that RDT is a more effective tool than history of fever to detect Malaria.

Conclusion

Malaria prevalence was high during POST-RS compared to PRE-RS. Using RDT to detect Malaria infection is more effective than history of fever in both PRE-RS and POST-RS. In PRE-RS, RDT has low positive predictive value and high negative predictive value for detection of Malaria cases. We recommend that a cost effectiveness analysis study be conducted for using RDT during PRE-RS and POST-RS.

Declarations

Ethics and consent statement

Ethical clearance was obtained from the Ghana Health Service Ethical Review Committee (GHS-ERC) with the approval identity (GHS-ERC: 14/05/15). Permission was also sought from the chiefs and elders of the Communities. Moreover, the parents/guardians of the children consented to be part of the study.

Consent for publication

Written informed consent was obtained from the study participants for publication of this research work. A copy of this form is available for review by the Editor of this journal.

Availability of data and material

Available upon request.

Funding

None

Conflict of interest

The authors declare that they have no competing interests.

Authors' Contributions

MK, conceived the study. MK and WT, EA and MA did the data analysis and wrote the methods section. MK, EA, WT and ET were...
responsible for the initial draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

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References


