Predictive performance of rapid diagnostic tests for falciparum malaria and its modelled impact on integrated community case management of malaria in sub-Saharan African febrile children

Johannes Mischlinger, PhD\textsuperscript{1,2}; Veronika Dudek, BSc\textsuperscript{1,2}, Michael Ramharter, Professor\textsuperscript{1,2*}

\textsuperscript{1} Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine & I. Dep. of Medicine, University Medical Center Hamburg-Eppendorf, Bernhard-Nocht-Straße 74
20359 Hamburg, Germany

\textsuperscript{2} German Centre for Infection Research (DZIF), partner site Hamburg-Luebeck-Borstel, Hamburg, Germany

*Corresponding author:

Michael Ramharter; E-mail: ramharter@bnitm.de, Telephone: +49 40 42818-511

Bernhard-Nocht-Str. 74, 20359, Hamburg, Germany

Key points

Community-based malaria case management programmes that only administer antimalarial treatments to each febrile child with a positive malaria-RDT result may not provide causative treatment in a high proportion of febrile children in the majority of malaria-endemic countries of Africa.
Abstract

Background

Integrated community case management (iCCM) of malaria complements and extends the reach of public health services to improve access to timely diagnosis and treatment of malaria. Such community-based programmes rely on standardised test-and-treat algorithms implemented by community health workers using malaria rapid diagnostic tests (RDTs). However, due to a changing epidemiology of fever causes, positive RDT results might not correctly reflect malaria-disease in all malaria-endemic settings in Africa. This study modelled diagnostic predictive values for all malaria-endemic African regions as an indicator of the programmatic usefulness of RDTs in iCCM campaigns on malaria.

Methods

Positive predictive values (PPV) and negative predictive values (NPV) of RDTs for clinical malaria were modelled. Assay-specific performance characteristics stem from the Cochrane Library and publicly available data on the proportion of malaria-attributable fevers among African febrile children under five years of age were used as prevalence matrix.

Results

Average country-level PPVs vary considerably: Ethiopia had lowest PPVs (HRP2-assay: 17.35%; pLDH-assay: 39.73%) and Guinea the highest PPVs (HRP2-assay: 95.32%; pLDH-assay: 98.46%). On the contrary, NPVs were above 90% in all countries (HRP2-assay: ≥94.87%; pLDH-assay ≥93.36%).
Conclusions

PPVs differed considerably within Africa when used for screening of febrile children indicating unfavourable performance of RDT-based test-and-treat algorithms in low-PPV settings. This suggests that the administration of antimalarials alone may not constitute causal treatment in the presence of a positive RDT result for a substantial proportion of patients particularly in low-PPV settings. Therefore, current iCCM algorithms should be complemented by information on other setting-specific major causes of fever.

Key words

malaria; RDT; integrated community case management; Africa
Background

Community management of malaria

In the past decade, community management approaches of malaria have become a cornerstone of various national programmes on malaria case management and malaria control [1,2]. Such approaches are centred on residents of a given community and usually complement the existing higher levels of health care infrastructure (e.g. district level hospitals, health care units etc). They entail recruitment and training of health workers who operate on the community level and thereby involve an increased accessibility of health care to the target population. There is diversity in how community-based approaches deliver care to the local population, ranging from home treatment approaches to offering adequate treatment in easily-accessible focal points (e.g. pharmacies, churches, schools etc.) [1,2]. Therefore, community health workers do not only bridge the gap between the formal health care system and the affected population, they also maintain some operational independence. Often, community management approaches are based on simple and clear algorithms to be followed by the community health worker on how to diagnose and treat malaria and when to refer a person to a higher level of the health care system [1]. In an attempt to simultaneously fight several major causes of childhood morbidity and mortality (i.e. most prominently pneumonia, diarrhoea and malaria) in lower- and middle-income countries, the WHO and UNICEF endorsed integrated community case management (iCCM) programmes [3].

Malaria rapid diagnostic tests (RDTs)

It is a WHO-endorsed policy that administration of antimalarial medication is preceded by a positive diagnostic test result for malaria [4]. Whereas microscopic detection of Plasmodium spp. in peripheral blood remains the gold standard diagnostic for case management, rapid diagnostic tests (RDTs) have increasingly become the backbone of malaria diagnostics in many malaria-endemic lower- and middle-income countries [5,6]. RDTs detect parasite-specific antigens in peripheral blood,
such as ‘histidin-rich protein II’ (HRP-2) and ‘parasite lactate dehydrogenase’ (pLDH) [7]. Diagnostic performance characteristics of RDTs to detect malaria were assessed systematically and described as favourable with sensitivities and specificities above 90% in malaria-endemic settings [8]. As part of iCCM programmes it is recommended to test all febrile children with a malaria RDT and to administer a dose of an effective antimalarial drug in the presence of a positive RDT result [3,4].

**Importance of diagnostic predictive values**

However, not every positive diagnostic test result truly indicates presence of disease [9]. The validity of diagnostic test results does not only depend on assay-specific characteristics of a diagnostic tool, but also relies on the prevalence of the condition of interest in the target population. The concept of predictive values combines assay-specific properties with properties of the respective target population [10]. The positive predictive value (PPV) indicates the probability of true disease in the presence of a positive diagnostic test result and the negative predictive value (NPV) the probability of absence of disease in the presence of a negative diagnostic test result. Therefore, predictive values provide more useful information for malaria case management algorithms on community level than the assay-specific properties of sensitivity and specificity.

As the transmission intensity of malaria affects the predictive performance of diagnostic test results, it is not understood how predictive values of malaria RDTs vary within sub-Saharan Africa [11,12]. This understanding is of importance to tailor test-and-treat algorithms of iCCM programmes of malaria in respective regions. In this study we modelled predictive values of RDTs to detect clinical malaria in children below five years of age in malaria-endemic regions in Africa. Based on this assessment we evaluate predictive values as proxy measure to estimate the effectiveness of current malaria RDT-based algorithms for the management of febrile children in iCCM programmes.
Methods

Computation of predictive values

Values for sensitivity and specificity were extracted from a meta-analysis that evaluated diagnostic RDT performance to diagnose falciparum malaria in endemic settings using expert light microscopy as gold standard [8]; the meta-analysis included 84 studies assessing performance characteristics of HRP-2-based assays and 20 studies assessing pLDH-based assays. HRP2-based RDTs have shown sensitivities and specificities of about 95.0% (95% CI: 93.5-96.2) and 95.2% (95% CI: 93.4-99.4), respectively to diagnose falciparum malaria in endemic populations and respective performance of pLDH-based RDTs are 93.2% (95% CI: 88.0-96.2%) and 98.5% (95% CI: 96.7-99.4) [8]. To date and to the best of our knowledge this study constitutes the best available evidence for conventional RDT-performance in endemic settings. Regions other than Africa and Plasmodium species other than *P. falciparum* were not considered in this analysis. Predictive values were ascertained via formulae according to Altman and Bland (Supplementary material) [9]:

Both predictive values have a dependency on the prevalence of the condition that they aim to detect [9,10]. PPVs decrease as the prevalence decreases, while NPVs decrease as prevalence increases. Both PPVs and NPVs depend on sensitivity and specificity, however, PPVs are especially impaired by low specificities and NPVs by low sensitivities (Supplementary figures 1 and 2).

Standardised malaria prevalence data from Malaria Atlas Project

The Malaria Atlas Project [Big Data Institute, University of Oxford, UK] constitutes a public and freely accessible database with epidemiological data related to malaria in Africa [13]. It allows visualisation of data in a cartesian coordinate system (heatmap) with a granularity of 5km*5km geographical area. Data were downloaded from the Malaria Atlas Project for malaria-endemic African countries.
on the ‘proportion of malaria-attributable fever among ≤ five-year-old children with fever (MAF)’ [11]. These data indicate the number of febrile episodes and its attributable fraction to malaria.

Modelling and data visualisation was performed in “R – Statistic” 3.5.1 (The R Project, University of Auckland, NZ) by using a dedicated R package facilitating access to Malaria Atlas Project data bases [14]. Predictive performance of RDTs was modelled on the basis of MAF and visualised as heat maps to highlight disparities of performance in as great detail as possible. Favourable RDT performance was highlighted in green colour and unfavourable RDT performance in red colour; yellow colour is in between the two extremes of green and red. A high proportion of MAF was allocated the colour red and a low proportion of MAF the colour blue. STATA/SE 15.1 (StataCorp, USA) was used to create supplementary figures allowing the depiction of scenarios of changing MAF prevalence or changing RDT performance characteristics.

**Interpretability of predictive performance of MAF models**

The ‘proportion of malaria-attributable fever among ≤ five-year-old children with fever’ (i.e. MAF dataset available in Malaria Atlas Project) were computed based on primary data from cross-sectional national household surveys conducted among children ≤ five years of age in African countries in 2014. As part of these surveys information on history of fever within the last two weeks was captured and a *Plasmodium falciparum*-specific RDT was performed in every child [11]. This information allowed the authors of the MAF dataset to compute the proportion of fevers among children aged ≤ five years on community level that are truly attributable to malaria (as opposed to children who are febrile due to other infections or other medical conditions, while at the same time harbouring an asymptomatic concomitant *Plasmodium* infection).
If MAF data are used as prevalence matrix and combined with meta-analytic performance characteristics of malaria RDTs the resulting predictive values demonstrate the probabilities that malaria is causally responsible (PPV) and not causally responsible (NPV) for fever in young febrile children in a malaria-endemic African community. Assuming that every child with a positive RDT receives an effective dose of artemisinin-combination therapy according to WHO guidelines, PPVs further constitute a proxy for appropriate (i.e. causal) fever case management on community level in malaria-endemic regions of Africa and provides a direct indication of over- or under-treatment of malaria based on the employed algorithm [5].

**Results**

**MAF values**

MAF data were available for 43 malaria-endemic countries of Africa (Table 1, Figure 1). 20.9% (9/43) of countries had a MAF value of at least 20%. 30.2% (13/43) of countries had a MAF value between 10-19.9% and 48.8% (21/43) of countries had a MAF value below 10%.

**Positive predictive values (PPVs)**

Average PPVs were highest in countries with high MAF values and lowest in countries with low MAF values for both HRP-2-based and pLDH-based assays and the respective distribution is depicted in figures 2 and 4. 27.9% (12/43) of countries had average HRP2-assay-based PPVs of above 80% and 7.0% (3/43) had PPVs of at least 90% (Table 1). 37.2% (16/43) of countries had HRP2-assay-based PPVs between 60-79.9%, 20.9% (9/43) between 40-59.9% and 14.0% (6/43) below 40%; Ethiopia had the lowest average HRP2-assay-based PPV at 17.35%. For iCCM programmes in which each positive HRP-2-based RDT result in a febrile child is followed by antimalarial treatment, findings suggest that in eleven (25.6%; 11/43) countries less than 50% of children treated with antimalarials would have
received causal treatment of their febrile condition. Concordantly, HRP-2-based RDT test-and-treat algorithms would lead to inappropriate diagnoses and eventually non-causative treatment in at least 50% of febrile children in these eleven countries.

72.1% (31/43) of countries had average pLDH-assay-based PPVs of above 80% and 44.2% (19/43) had PPVs of at least 90%. 18.6% (8/43) of countries had pLDH-assay-based PPVs between 60-79.9%, 7.0% (3/43) between 40-59.9% and 2.3% (1/43) below 40%; Ethiopia had the lowest average pLDH-assay-based PPV at 39.73%. Again, for iCCM programmes in which each positive pLDH-based RDT in a febrile child is followed by antimalarial treatment, findings suggest that in only two (4.7%; 2/43) countries adequate diagnosis and causal treatment was given in less than 50% of febrile children. Concordantly, pLDH-based RDT test-and-treat algorithms would lead to misclassification and potential non-causative treatment of at least 50% of febrile children in these two countries.

Negative predictive values (NPVs)

Concordantly, average NPVs were lowest in countries with high MAF values and highest in countries with low MAF values (Figures 3 and 5). 72.1% (31/43) of countries had average HRP2-assay-based NPVs of above 99.0% and 97.7% (42/43) had an NPV of above 95.0% (Table 1). Guinea had the lowest average HRP2-assay-based NPV with 94.86%. 55.8% (24/43) of countries had average pLDH-assay-based NPVs of above 99.0% and 97.7% (42/43) had an NPV of above 95.0%. Guinea had the lowest average pLDH-assay-based NPV with 93.36%. Assuming that each negative test result leads to no antimalarial treatment, under-treatment is estimated to occur in less than 5% of febrile children in all observed countries, except for Guinea, where under-treatment of febrile children was estimated to be 5.14% for HRP-2-based test-and-treat algorithms and 6.64% for pLDH-based algorithms.
Discussion

In iCCM programmes common life-threatening conditions in children, such as pneumonia, diarrhoea and malaria, are managed early-on at the community level by community health workers with basic medical training [3,5]. With the advent of more sensitive and specific malaria RDTs initially simple case management algorithms received an additional layer of complexity, namely that effective antimalarials should only be administered in the presence of a positive malaria RDT result [3,15]. Therefore, the presented predictive values hold great importance for official iCCM programmes as they estimate the validity of respective RDT-based test-and-treat algorithms. PPVs importantly rely on malaria transmission intensity which consecutively affects MAF data. To ensure up-to-date estimates of PPVs it is recommended that MAF data are produced periodically and are publicly accessible. This may ultimately impact on treatment algorithms of iCCM programmes. It is of mention that the focus of this manuscript is on *P. falciparum* and therefore, its generalisability will likely not extend to regions of high *P. vivax* endemicity, such as regions in East Africa (e.g. Ethiopia).

Overall NPVs were highly favourable for both HRP2-based and pLDH-based assays and for virtually all malaria-endemic regions of Africa. This indicates that malaria is extremely unlikely as fever-causing factor in febrile children with a negative malaria RDT result and supports adherence to non-administration of antimalarials by community health workers in the presence of a negative RDT. Instead, referral to higher levels of the health care sector is promoted where alternative fever causes can be assessed [5]. On the contrary, PPVs presented in this study highlight that a positive RDT result may not truly mirror malaria as the cause of fever in febrile children ≤ five years of age in virtually all evaluated countries of sub-Saharan Africa – globally the region of highest malaria case burden [5]. This implies that the administration of antimalarials alone may not constitute causal treatment particularly in low-PPV settings. Thus, in low-PPV settings it becomes increasingly important to investigate alternative causes of fever even despite positive RDT results. Dedicated iCCM
programmes aiming at delivering simple and standardised management of childhood illnesses may need to reflect the overall low PPV to avoid misdiagnosis and withholding of appropriate medical management. Furthermore, algorithms should be best complemented by regional epidemiological data on non-malaria-related causes of fever. Given the more favourable PPVs for pLDH-based RDTs than HRP2-based RDTs with NPVs being comparably high, usage of pLDH-based assays might be advocated in RDT-based test-and-treat approaches.

Scenarios of falling and rising prevalence of malaria-attributable fevers

As consequence of a changing malaria epidemiology and concurrent epidemics of newly emerging diseases, scenarios need to be envisioned that simulate changing MAF prevalences [5,16,17]. Furthermore, MAF prevalences might be subjected to seasonal variations.

Scenario of decreasing MAF prevalence

Given constant values of sensitivity and specificity of an RDT a falling MAF prevalence will decrease PPVs and thereby the validity of test-and-treat based algorithms of iCCM programmes. Such a scenario highlights the need for highly specific testing methods to corroborate malaria diagnosis; pLDH-based assays carry higher specificity than HRP2-based assays and may therefore be preferable. On the other hand, NPVs may become even more valid, as theory indicates rising NPVs in the wake of a falling prevalence (Supplementary figures 1 and 2). Concordantly, the proportion of undertreated febrile children will decrease.

Scenario of increasing MAF prevalence

Given constant values of sensitivity and specificity a rising MAF prevalence will increase PPVs and thereby the validity to which a positive RDT result reflects the causal reason for fever in a febrile child. On the other hand, a rising MAF prevalence will impair NPVs thus potentially affecting the validity of negative test results. However, NPVs of an RDT with 95% sensitivity and specificity would
only drop below 90% if prevalence increased to about 68% of the tested population (Supplementary figures 1 and 2).

Scenarios of changing assay-specific characteristics

Increasing sensitivity

Next generation RDTs have been described as capable of detecting parasite blood densities that are about ten-fold lower than the lower limit of detection of conventional RDTs [18,19]. Their role might be most important in large-scale malaria screening programmes aiming at eliminating malaria from certain settings. However, it is not clear yet, whether this new RDT generation might contribute to improved case management of malaria-diseased individuals. A hospital-based study conducted in Ghana (n=4169), which investigated the causes of paediatric febrile illnesses, found that the frequency of gastrointestinal, lower respiratory tract and bloodstream infections became increasingly common as malaria parasite density decreased [12]. For malaria-endemic settings this indicates that the causal factors of fever in hospitalised paediatric patients is often an infectious cause other than a concomitant (‘non-fever-causing’) malaria parasitaemia. This holds particularly true for children and adolescents of an age with likely established semi-immunity against malaria [20]. In order to gain additional diagnostic information of causes of fever, the importance of exact quantification of malaria parasitaemia by microscopy has been highlighted, as higher levels of parasitaemia are more indicative for a symptomatic malaria episode [6,12]. In that regard the development of semi-quantitative RDTs has been identified as a potential improvement for medical management. On the contrary, potential implementation of highly sensitive next-generation RDTs with a ten-fold lower limit of detection (i.e. increased sensitivity) may counter-intuitively lead to less favourable diagnostic performance when used in dedicated iCCM programmes. Certainly, it would lead to more diagnoses of *Plasmodium* infections and thereby aiding in malaria elimination efforts, however, not aiding to correctly identify causes of fever in febrile children.
Decreasing sensitivity
HRP-2 deletions have been described as the cause for some false-negative HRP-2-based test results (i.e. decreasing sensitivity of HRP-2-based assays) and it is not clear how this might affect overall test performance in Africa in the future [21]. However, it might not considerably affect management of febrile children with positive test results, as PPVs are much more robust to drops in sensitivity than to drops in specificity. Theory indicates that NPVs are not significantly affected by decreases of assay sensitivity in the presence of low MAF prevalences (Supplementary figure 2). However, unlike for overtreatment the consequences of undertreatment are potentially lethal. Therefore, in case of large-scale spread of HRP-2 deletions, RDTs should be used whose performance is unaffected by HRP-2 deletions (e.g. pLDH-based).

Decreasing specificity
RDT-detectable antigens can persist after successful treatment for a certain period, which can impair specificity of subsequent testing with RDTs [22]. Therefore, iCCM programmes might potentially be able to increase the specificity of their testing algorithms by capturing any history of recent antimalarial treatment. However, diagnostic performance data used in this manuscript stem from a meta-analysis that included numerous studies that also recruited participants with history of recent malaria treatment; this suggests generalisability onto individuals with recent history of antimalarial treatment.

Conclusions
The prevalence of malaria-attributable fevers among febrile African children aged ≤ five years has decreased over the last decade leading to a decline of the validity of positive RDT results represented by low PPVs for many African settings. Consequently, iCCM programmes that
administer antimalarial treatments to each febrile child with a positive malaria-RDT may not provide causative treatment in the majority of febrile children in settings of low PPVs. On the contrary, NPVs were comparatively high supporting the use of RDTs in community-based programmes for decisions to withhold antimalarials in case of a negative RDT result. Africa-wide heatmaps depicting predictive performance of RDTs hold important information for potential modification of algorithms for community health workers on fever management in settings of unfavourable PPV performance. Due to higher specificity pLDH-based assays might be preferable to HRP-2-based assays leading to higher PPVs and a higher validity of test-and-treat algorithms of iCCM programmes. Such algorithms should be complemented by information on other setting-specific major causes of fever.
NOTES

Author’s contribution

JM and MR had the idea for the manuscript. JM and VD performed analyses of the project and VD visualised the data. All authors contributed to writing of the manuscript. All data used for this study has been publicly accessible.

Declaration of interests

The authors have no interest to declare.
References

1. World Health Organization. Malaria case management: operations manual. 2009. Available at: https://www.who.int/malaria/publications/atoz/9789241598088/en/. Accessed 22 July 2020.

2. World Health Organization. Community-based reduction of malaria transmission. Consultation Report. 2012. Available at: https://www.who.int/malaria/publications/atoz/9789241502719/en/. Accessed 22 July 2020.

3. World Health Organization. An equity-focused strategy to improve access to essential treatment services for children. 2012. Available at: https://www.who.int/maternal_child_adolescent/documents/iccm_service_access/en/. Accessed 28 April 2020.

4. World Health Organization. Guidelines for the treatment of malaria. Third edition. 2015. Available at: https://www.who.int/malaria/publications/atoz/9789241549127/en/.

5. World Health Organization. World Malaria Report 2019. 2019. Available at: https://www.who.int/publications-detail/world-malaria-report-2019.

6. Mischlinger J, Pitzinger P, Veletzky L, et al. Validity and reliability of methods to microscopically detect and quantify malaria parasitaemia. Trop Med Int Health 2018; 23:980–991.

7. Murray CK, Gasser RAJ, Magill AJ, Miller RS. Update on rapid diagnostic testing for malaria. Clin Microbiol Rev 2008; 21:97–110.

8. Abba K, Deeks JJ, Olliaro P, et al. Rapid diagnostic tests for diagnosing uncomplicated P. falciparum malaria in endemic countries. Cochrane database Syst Rev 2011; :CD008122.

9. Altman DG, Bland JM. Diagnostic tests 2: Predictive values. BMJ 1994; 309:102.
10. Mischlinger J, Schernhammer E. A common trap of diagnostic tests: Disease prevalence and positive predictive value. Wien. Klin. Wochenschr. 2017; 129:583–584.

11. Dalrymple U, Cameron E, Bhatt S, Weiss DJ, Gupta S, Gething PW. Quantifying the contribution of Plasmodium falciparum malaria to febrile illness amongst African children. Elife 2017; 6.

12. Hogan B, Eibach D, Krumkamp R, et al. Malaria Coinfections in Febrile Pediatric Inpatients: A Hospital-Based Study From Ghana. Clin Infect Dis 2018; 66:1838–1845.

13. Guerra CA, Hay SI, Lucioparedes LS, et al. Assembling a global database of malaria parasite prevalence for the Malaria Atlas Project. Malar J 2007; 6:17.

14. Pfeffer DA, Lucas TCD, May D, et al. malariaAtlas: an R interface to global malariometric data hosted by the Malaria Atlas Project. Malar J 2018; 17:352.

15. Mabey D, Vos T. Syndromic approaches to disease management. Lancet 1997; 349:S26–S28. Available at: https://doi.org/10.1016/S0140-6736(97)90085-4.

16. Kamorudeen RT, Adedokun KA, Olarinmoye AO. Ebola outbreak in West Africa, 2014-2016: Epidemic timeline, differential diagnoses, determining factors, and lessons for future response. J Infect Public Health 2020; 13:956–962.

17. Lone SA, Ahmad A. COVID-19 pandemic - an African perspective. Emerg Microbes Infect 2020; 9:1300–1308.

18. Slater HC, Ross A, Ouedraogo AL, et al. Assessing the impact of next-generation rapid diagnostic tests on Plasmodium falciparum malaria elimination strategies. Nature 2015; 528:S94-101.

19. Pham NM, Karlen W, Beck H-P, Delamarche E. Malaria and the ‘last’ parasite: how can technology help? Malar J 2018; 17:260.
20. Mischlinger J, Ronnberg C, Alvarez-Martinez MJ, et al. Imported Malaria in Countries where Malaria Is Not Endemic: a Comparison of Semi-immune and Nonimmune Travelers. Clin Microbiol Rev 2020; 33.

21. Poti KE, Sullivan DJ, Dondorp AM, Woodrow CJ. HRP2: Transforming Malaria Diagnosis, but with Caveats. Trends Parasitol 2020; 36:112–126.

22. Foundation for Innovative New Diagnostics (FIND). How To Use a Rapid Diagnostic Test (RDT) - A guide for training at a village and clinic level. 2012. Available at: https://www.finddx.org/wp-content/uploads/2016/03/paracheck_pf_manual_rev1_032612.pdf. Accessed 20 November 2020.
Figures

Figure 1: Proportion of malaria-attributable fevers among all febrile children ≤ five years of age. PR ...

Prevalence

Figure 2: HRP-2-based malaria rapid diagnostic tests (RDTs). Positive predictive values (PPVs) reflect the probability of malaria as causal reason for fever in the presence of a positive test result in children aged ≤ five years. Probability measure from 0 to 1. Sens ... Sensitivity; Spec ... Specificity

Figure 3: HRP-2-based malaria rapid diagnostic tests (RDTs). Negative predictive values (NPVs) reflect the probability that malaria is not the causal reason for fever in the presence of a negative test result in children aged ≤ five years. Probability measure from 0 to 1. Sens ... Sensitivity; Spec ... Specificity

Figure 4: pLDH-based malaria rapid diagnostic tests (RDTs). Positive predictive values (PPVs) reflect the probability of malaria as causal reason for fever in the presence of a positive test result in children aged ≤ five years. Probability measure from 0 to 1. Sens ... Sensitivity; Spec ... Specificity

Figure 5: pLDH-based malaria rapid diagnostic tests (RDTs). Negative predictive values (NPVs) reflect the probability that malaria is not the causal reason for fever in the presence of a negative test result in children aged ≤ five years. Probability measure from 0 to 1. Sens ... Sensitivity; Spec ... Specificity
### Table 1: Average predictive values per country

| MAF% | HRP-2-based RDTs | pLDH-based RDTs |
|------|-------------------|-----------------|
|      | PPV% (95% CI)     | NPV% (95% CI)   | PPV% (95% CI) | NPV% (95% CI) |
| Angola | 8.26 | 64.05 (56.05 - 93.52) | 99.52 (99.37 - 99.65) | 84.83 (70.59 - 93.52) | 99.38 (98.89 - 99.65) |
| Benin  | 18.69 | 81.97 (76.5 - 97.35) | 98.8 (98.42 - 99.12) | 93.45 (85.97 - 97.35) | 98.43 (97.22 - 99.12) |
| Botswana | 1.28 | 20.42 (15.51 - 67.52) | 99.93 (99.9 - 99.95) | 44.61 (25.69 - 67.52) | 99.91 (99.83 - 99.95) |
| Burkina Faso | 15.82 | 78.81 (72.69 - 96.78) | 99.02 (98.7 - 99.28) | 92.11 (83.36 - 96.78) | 98.71 (97.72 - 99.28) |
| Burundi | 7.86 | 62.8 (54.72 - 93.18) | 99.55 (99.4 - 99.67) | 84.12 (69.46 - 93.18) | 99.41 (98.95 - 99.67) |
| Cameroon | 19.71 | 82.93 (77.66 - 97.52) | 98.72 (98.32 - 99.07) | 93.84 (86.74 - 97.52) | 98.33 (97.04 - 99.07) |
| Central African Republic | 27.99 | 88.49 (84.63 - 98.42) | 97.99 (97.36 - 98.53) | 96.02 (91.2 - 98.42) | 97.38 (95.39 - 98.53) |
| Chad  | 7.35 | 61.09 (52.91 - 92.71) | 99.58 (99.45 - 99.69) | 93.84 (86.74 - 97.52) | 98.33 (97.04 - 99.07) |
| Congo  | 17.94 | 81.22 (75.59 - 97.22) | 98.86 (98.5 - 99.17) | 93.14 (85.35 - 97.22) | 98.51 (97.35 - 99.17) |
| Côte d'Ivoire | 22.42 | 85.11 (80.36 - 97.88) | 98.5 (98.02 - 98.9) | 94.72 (88.51 - 97.88) | 98.04 (96.53 - 98.9) |
| Democratic Republic of the Congo | 14.78 | 77.43 (71.07 - 96.52) | 99.09 (98.8 - 99.34) | 91.5 (82.22 - 96.52) | 98.81 (97.89 - 99.34) |
| Djibouti | 3.63 | 42.7 (34.79 - 85.79) | 99.8 (99.73 - 99.85) | 70.06 (50.11 - 85.79) | 99.74 (99.53 - 99.85) |
| Equatorial Guinea | 41.44 | 93.33 (90.92 - 99.12) | 96.41 (95.3 - 97.36) | 97.77 (94.96 - 99.12) | 95.34 (91.92 - 97.36) |
| Eritrea | 6.14 | 56.42 (48.09 - 91.29) | 99.65 (99.54 - 99.75) | 80.25 (63.56 - 91.29) | 99.55 (99.19 - 99.75) |
| Country        | Value | Range        | 1999 (%) | Range        | 1999 (%) | Range        | 1999 (%) | Range        | 1999 (%) |
|----------------|-------|--------------|----------|--------------|----------|--------------|----------|--------------|----------|
| Ethiopia       | 1.05  | 17.35 (13.06 - 62.98) | 99.94 (99.92 - 99.95) | 39.73 (22.05 - 62.98) | 99.92 (99.86 - 99.95) |
| Gabon          | 9.96  | 68.64 (61.04 - 94.66) | 99.42 (99.23 - 99.57) | 87.29 (74.68 - 94.66) | 99.24 (98.64 - 99.57) |
| Gambia         | 2.05  | 29.28 (22.86 - 77.04) | 99.89 (99.85 - 99.92) | 56.52 (35.81 - 77.04) | 99.85 (99.74 - 99.92) |
| Ghana          | 30.4  | 89.63 (86.08 - 98.59) | 97.75 (97.04 - 98.35) | 96.44 (92.09 - 98.59) | 97.07 (94.85 - 98.35) |
| Guinea         | 50.74 | 95.32 (93.58 - 99.39) | 94.86 (93.31 - 96.21) | 98.46 (96.48 - 99.39) | 93.36 (88.66 - 96.21) |
| Guinea-Bissau  | 13.7  | 75.85 (69.22 - 96.21) | 99.17 (98.9 - 99.39) | 90.79 (80.89 - 96.21) | 98.91 (98.06 - 99.39) |
| Kenya          | 2.22  | 31 (24.33 - 78.44)   | 99.88 (99.84 - 99.91) | 58.51 (37.71 - 78.44) | 99.84 (99.71 - 99.91) |
| Liberia        | 13.48 | 75.51 (68.82 - 96.15) | 99.18 (98.92 - 99.4)  | 90.63 (80.6 - 96.15)  | 98.93 (98.1 - 99.4)  |
| Madagascar     | 8.49  | 64.74 (56.79 - 93.7) | 99.51 (99.35 - 99.64) | 85.21 (71.21 - 93.7)  | 99.36 (98.86 - 99.64) |
| Malawi         | 14.16 | 76.55 (70.03 - 96.35) | 99.14 (98.86 - 99.37) | 91.11 (81.47 - 96.35) | 98.87 (97.99 - 99.37) |
| Mali           | 12.59 | 74.03 (67.11 - 95.84) | 99.24 (99 - 99.45)    | 89.94 (79.34 - 95.84) | 99.01 (98.24 - 99.45) |
| Mauritania     | 2.61  | 34.65 (27.51 - 81.12) | 99.85 (99.81 - 99.89) | 62.47 (41.67 - 81.12) | 99.81 (99.66 - 99.89) |
| Mozambique     | 35.88 | 91.71 (88.79 - 98.89) | 97.14 (96.25 - 97.9)  | 97.2 (93.71 - 98.89)  | 96.28 (93.5 - 97.9)  |
| Namibia        | 2.64  | 34.92 (27.75 - 81.29) | 99.85 (99.81 - 99.89) | 62.75 (41.96 - 81.29) | 99.81 (99.66 - 99.89) |
| Niger          | 4.82  | 50.05 (41.77 - 89.03) | 99.73 (99.64 - 99.8)  | 75.88 (57.45 - 89.03) | 99.65 (99.37 - 99.8)  |
| Nigeria        | 13.45 | 75.46 (68.76 - 96.14) | 99.19 (98.93 - 99.4)  | 90.61 (80.56 - 96.14) | 98.93 (98.1 - 99.4)  |
| Rwanda         | 6.98  | 59.76 (51.52 - 92.32) | 99.6 (99.48 - 99.71)  | 82.33 (66.67 - 92.32) | 99.48 (99.07 - 99.71) |
| Senegal        | 4.32  | 47.19 (39.01 - 87.86) | 99.76 (99.68 - 99.82) | 73.72 (54.62 - 87.86) | 99.68 (99.44 - 99.82) |
| Sierra Leone   | 20.18 | 83.34 (78.17 - 97.59) | 98.68 (98.27 - 99.04) | 94.01 (87.08 - 97.59) | 98.28 (96.95 - 99.04) |
| Somalia        | 8.8   | 65.63 (57.75 - 93.92) | 99.49 (99.33 - 99.63) | 85.7 (72.01 - 93.92)  | 99.33 (98.81 - 99.63) |
| South Africa   | 6.58  | 58.22 (49.94 - 91.86) | 99.63 (99.51 - 99.73) | 81.89 (65.25 - 91.86) | 99.51 (99.13 - 99.73) |
| South Sudan    | 13.15 | 74.97 (68.2 - 96.04)  | 99.21 (98.95 - 99.42) | 90.39 (80.14 - 96.04) | 98.96 (98.15 - 99.42) |
| Country  | MAF  | HRP-2 (%) (95% CI) | PPV (%) (95% CI) | NPV (%) (95% CI) |
|---------|------|--------------------|------------------|-----------------|
| Sudan   | 3.86 | 44.27 (36.25 - 86.55) | 99.78 (99.72 - 99.84) | 71.38 (51.7 - 86.55) |
| Swaziland | 4.11 | 45.89 (37.78 - 87.29) | 99.77 (99.7 - 99.83) | 72.7 (53.33 - 87.29) |
| Tanzania | 10.64 | 70.2 (62.78 - 95.02) | 99.37 (99.17 - 99.54) | 88.09 (76.04 - 95.02) |
| Togo    | 26.41 | 87.65 (83.56 - 98.29) | 98.14 (97.56 - 98.64) | 95.7 (90.53 - 98.29) |
| Uganda  | 10.06 | 68.88 (61.3 - 94.71) | 99.41 (99.22 - 99.57) | 87.42 (74.89 - 94.71) |
| Zambia  | 20.52 | 83.63 (78.52 - 97.64) | 98.66 (98.23 - 99.02) | 94.13 (87.31 - 97.64) |
| Zimbabwe | 4.48  | 48.13 (39.91 - 88.26) | 99.75 (99.67 - 99.82) | 74.45 (55.56 - 88.26) |

Abbreviations: MAF ... proportion of malaria-attributable fever among febrile children aged ≤ five years; HRP-2: histidin-rich protein II; pLDH: parasite lactate dehydrogenase; PPV ... positive predictive value; NPV ... negative predictive value
Figure 4
