

SHIFTING FROM PRESUMPTIVE TO TEST-BASED MANAGEMENT OF MALARIA – TECHNICAL BASIS AND IMPLICATIONS FOR MALARIA CONTROL IN GHANA

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SUMMARY

The presumptive approach was the World Health Organisation (WHO) recommended to the management of malaria for many years and this was incorporated into syndromic guidelines such as the Integrated Management of Childhood Illnesses (IMCI). In early 2010 however, WHO issued revised treatment guidelines that call for a shift from the presumptive to the test-based approach. Practically, this implies that in all suspected cases, the diagnosis of uncomplicated malaria should be confirmed using rapid test before treatment is initiated. This revision effectively brings to an end an era of clinical practice that span several years. Its implementation has important implications for the health systems in malaria-endemic countries. On the basis of research in Ghana and other countries, and evidence from program work, the Ghana National Malaria Control Program has issued revised national treatment guidelines that call for implementation of test-based management of malaria in all cases, and across all age groups. This article reviews the evidence and the technical basis for the shift to test-based management and examines the implications for malaria control in Ghana.

Keywords: malaria, presumptive diagnosis, test-based diagnosis, fever, Ghana

INTRODUCTION

Malaria causes an estimated 660 000 deaths annually and remains a major cause of morbidity and mortality in high-endemic countries.¹ Traditionally, two approaches have been adopted in the management of malaria: presumptive and test-based.

The presumptive approach relies solely on clinical symptoms and signs to establish diagnosis and initiate treatment. In contrast, the test-based approach requires confirmation, either parasitological or antigen-antibody test, before the diagnosis of malaria can be made, and treatment initiated.

For many years, the World Health Organisation (WHO) recommended the presumptive approach and this was implemented across countries in malaria-endemic, sub-Saharan Africa. In early 2010 however, WHO issued revised treatment guidelines that call for a shift from presumptive to test-based approach. This revision to the guidelines effectively brings to an end the practices of several decades.²⁻⁴ This article reviews the evidence-base for the shift to the test-based approach, and examines implications of its implementation in Ghana.

Justifications for the presumptive diagnosis of malaria

The major justifications for the presumptive approach to managing malaria in high-endemic countries were: (1) The high levels of transmission and associated morbidity and mortality; (2) The availability of affordable, yet effective antimalarials; (3) The lack of appropriate diagnostic tools.⁵⁻⁸

High transmission, and associated levels of morbidity and mortality

For many years, in high-transmission settings malaria was considered to be either the primary cause of all febrile illnesses or a major contributory factor.^{7, 9-11} Studies from sub-Saharan Africa suggested that asymptomatic parasitaemia in children in high-transmission settings could be as high as 71% in under-five children¹², and between 37% and 68% in children aged

up to ten years of age.^{13, 14} A hospital-based study in Kenya in 1996 found that up to 45% of children admitted with respiratory signs (indicative of severe ARI) had malaria as the primary diagnosis.¹⁵ In Ghana and Kenya, the probability of fever that could be attributed to malaria was found to be as high as 61% and 67% respectively.^{16, 17}

Up to half of all mortality among African children aged 6 months to 5 years was considered to be due to malaria¹⁸ and nearly 3% of disability adjusted life years was attributed to malaria mortality globally.¹⁹

With such high levels of malaria-related morbidity and mortality, it was considered neither cost-effective nor safe to routinely distinguish malaria from non-malaria cases, and restrict antimalarial drugs to only confirmed cases, particularly where the attempt to do so could lead to rapid clinical deterioration and possibly death. The evidence supported the use of fever as a proxy indicator of malaria in both clinical care and epidemiological surveys.^{7, 20, 21}

Availability of affordable, yet effective antimalarials

The availability of affordable, yet effective antimalarials such as chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) was another important justification for the presumptive approach. Both were effective first-line antimalarial drugs in endemic countries in sub-Saharan Africa for many years. Being synthetic products, CQ and SP were cheap to produce and were affordable. They were also safe to use, including as chemoprophylaxis in pregnant women. Drug pressure exerted through their use in the presumptive treatment of uncomplicated malaria²² contributed to development of resistance.

In 2004, Ghana joined many countries across sub-Saharan Africa in changing its first-line drug for the treatment of uncomplicated malaria from chloroquine to artemisinin-based combination treatments. Reports of resistance and or prolonged parasite clearance associated with use of the artemisinins in Western Cambodia, and along the Thailand-Myanmar (Burma) border raise concern about the need to protect the ACTs from unwarranted use.²³⁻²⁵

Lack of appropriate diagnostic tools

The lack of easy-to-use, accurate and reliable malaria diagnostic tools was another important justification for adoption of the presumptive approach.^{7, 26, 27} Blood smear microscopy using Giemsa stain techniques which had been the mainstay of parasitological confirmation of malaria for many years, was too elaborate, technical, and expensive to set-up and maintain in all primary care facilities and was time-consuming. Elec-

tricity or an alternate source of power, and clean water is needed, neither of which are reliably available in most parts of sub-Saharan Africa where primary care facilities are situated.²⁸⁻³⁰ The availability of skilled microscopists to prepare and read slides accurately and reliably is an added challenge in low and middle-income countries.^{31, 32}

A diagnostic tool that could be easily and rapidly applied to many patients within a short time was needed. Such a diagnostic test needed to be one that both professional and non-professional health workers could perform.

Presumptive management of malaria formed the basis of the treatment of malaria within the Integrated Management of Childhood Illnesses (IMCI) where all under-five children who presented with fever were prescribed an antimalarial.⁷

Arguments for and against the shift

It is now argued that the presumptive approach is no longer justifiable and there is a need to shift to the test-based approach.³³⁻³⁵ However, the decision to shift from presumptive to test-based approach in managing malaria has occasioned considerable debate.^{6, 36-38} Those who favoured the shift to test-based management of malaria argued that the factors that justified the presumptive approach were no longer valid. Malaria transmission, originally high, has been declining and affordable antimalarials were no longer effective and had been replaced with the more expensive artemisinin-based combination therapy (ACT). They also argued that smear microscopy was no longer the only practical means of confirming the diagnosis of malaria at the point of care due to the availability of malaria rapid diagnostic tests (mRDTs). Those who favoured the shift further argued that test-based approach would lead to improvement in the management of non-malaria febrile illnesses.³³

Those who opposed the shift to test based management argued that there was insufficient evidence that malaria was on a sustainable decline. They questioned the capacity of malaria-endemic country health systems to sustain stock of quality-assured RDTs. They further believed that there was insufficient evidence on the safety of restricting ACT to test-positive cases and that a policy of test-based management of malaria would not necessarily lead to improvement in the management of non-malarial febrile illnesses.^{38, 39}

In evaluating the appropriateness of implementing the shift to test-based management of malaria in Ghana, it is important to assess whether local and sub-regional

evidence, supports the decline of malaria and whether the available RDTs are accurate and reliable.

Is malaria on a sustainable decline?

Recent reports suggest that the burden of malaria is declining in many areas of sub-Saharan Africa.^{40, 41} According to the 2010 and 2011 World Malaria Reports, appreciable progress was made between 2000 and 2010 to reduce the burden of malaria globally. A 26% decline in malaria deaths was recorded globally, with sub-Saharan Africa accounting for 33% of this decline.

In the same period, the number of malaria cases per 1000 persons at risk declined by about 17%.^{42, 43} Between 1985-1999 and 2000-2007, *Plasmodium falciparum* prevalence rates among children aged 2 to 10 years in sub-Saharan Africa declined from 37% in 1985-1999 to 17% in 2000-2007.^{14, 33}

related admissions, blood transfusions, and malaria-attributed mortality declined by 77%, 67% and 75% respectively. A further 10-fold reduction in malaria parasite prevalence was achieved in that country in 2006 after the introduction of long-lasting insecticidal nets.⁴⁴ In The Gambia, findings from a retrospective analysis of records on numbers and proportions of malaria in-patients, deaths, blood-slide examinations at five health facilities over periods ranging from 7 years to 9 years has suggested that a “large proportion of the burden of malaria in that country has been alleviated.”⁴⁵ In Uganda, a study in four districts in 2007 found dramatically lower-than-expected levels of parasitaemia among children with fever presenting to health facilities. Parasitaemia ranged from 13.9% in patients ≥ 5 years in medium-to-high transmission areas to 50.5% for children < 5 years in very high transmission areas. These districts had historically been known to record some of the highest entomological inoculation rates (between 564 and 1,564 infective bites per person per year) in the world.⁴⁶ Table 1 provides examples of recent reports of reduction in the burden of malaria in sub-Saharan Africa and the factors reported to be underlying the reductions.

Ghana is classified as being high malaria-transmission. Evidence is however emerging about substantial reduction in malaria transmission in the country. The findings of the recent Multiple Indicator Cluster Survey (MICS) confirm dramatically low levels of malaria parasitaemia among under-five children across the country. The proportions of under-five children found to have parasitaemia ranged from as low as 4% in Accra to 51% in the Upper-West region (Figure 1).⁴⁷ These findings contrast with much higher prevalence recorded in similar surveys in the past.^{12, 48}

The National Malaria Programme (NMCP) is in the process of establishing sentinel sites across the country where all febrile cases presenting to sentinel facilities will be tested and malaria parasitaemia recorded will be used as a proxy indicator of levels of malaria transmission. Research into the development of alternative simple tools for monitoring the burden of malaria in Ghana is also underway.

Are accurate and reliable RDTs available?

Although mRDTs were developed in the early 1990s, their use in routine health services was limited by the lack of international standards for comparing the different brands. Malaria programs had no evidence base to guide procurement decisions. The WHO/FIND/CDC-supported program for testing commercially available RDT products and ranking them according to performance now provides this evidence.

MALARIA PARASITE PREVALENCE IN GHANA, 2012

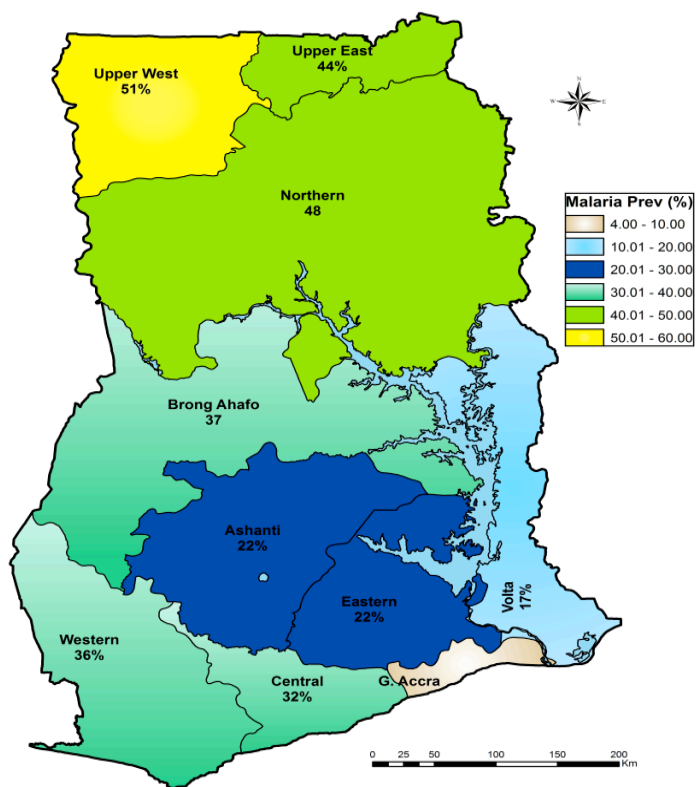


Figure 1 Prevalence of malaria parasitaemia among under-five children in the ten regions of Ghana (Source: MICS 2011⁴⁷)

In Zanzibar, data from routine health services and clinico-parasitological surveys have been used to demonstrate that between 2002 and 2006, malaria-

Table 1 Examples of studies that report reduction in the burden of malaria in sub-Saharan Africa.

Country	Study Design	Character of site	Reported reduction	Observed period of decline	Control or comparator		Adjustment for Rain-fall	Time of deployment relative to evidence of malaria decline			Reported Reasons
					Non-malarial cases	Non-intervention area or prior data		ACT	ITN	IRS	
Coastal Kenya ⁷⁷	Retrospective review of routine HMIS data	One routinely researched site and two adjoining non-research sites	63%, 53% and 28% reduction in malaria cases in 3 district hospitals	1999, 2006	Yes	Yes	Yes	After	After	Not deployed	Malaria control interventions
Ifakara, Tanzania ⁷⁸	Retrospective review of data from cohort studies	Routinely researched site	Reduced from 0.8 to 0.43 episodes per child per year	1995-2000	Yes	No	No	After	After. Net used before were mostly untreated and at coverage less than 20%	Not deployed	Economic improvements, liberalization of health sector and malaria control interventions
Zanzibar, Tanzania ⁴⁴	Before and After intervention	Not routinely researched	77% reduction in malaria admissions	2003-2005	No	Yes	Yes	Before	Before	After	Artemisinin combination Therapy and Insecticide Treated Nets
Mozambique, South Africa and Swaziland ⁷⁹	Before and After intervention	Not routinely researched	> 60% fall in parasite prevalence in all 3 zones studied	1999-2005	No	Yes	No	After	Not deployed	Before	Indoor residual spraying
Guinea-Bissau ⁸⁰	Comparative, Cross-sectional	Routinely researched site	Reduced from 44–79% to 3%	1994, 1999, 2003-4	No	Yes	No**	After	After. Only 5% of nets used before were treated	Not deployed	Untreated bed nets and urbanization
Eritrea ⁸¹	Before (Retrospective review of routine HMIS data) and After (cross-sectional survey) intervention	Not routinely researched	Decrease in malaria incidence of 83.3% and case fatality by from 0.21 to 0.14%	2000-4	No	Yes	No***	Not deployed	Before	Before	Climate change and malaria control methods (ITNs, IRS and early case detection and treatment)
Rwanda and Ethiopia ⁸²	Before and After intervention	Not routinely researched	55% and 73% fall in under-5 in-patient cases in Rwanda & Ethiopia	2001-7	Yes	Yes	No	Before	Before	Not deployed. Used routinely before and after in Ethiopia	Stronger correlation with ACT and ITN scale-up in Rwanda. Less firmer in the case of Ethiopia due to epidemic nature of transmission
Senegal ⁸³	Prospective. Nested in clinical trial	Not routinely researched.	Incidence rate from 46.1% to 37.5%	1998 - 2002	No	No	No***	Before	Not deployed	Not deployed	None particularly ACT considered unlikely
Tanzania ⁸⁴	Before and After intervention	Not routinely researched	4-6-fold reduction in EIR,	1990-4 to 2001-3	No	Yes	No	Not deployed	Before	Not deployed	Deployment of both treated and untreated nets)
South Africa ⁸⁵	Retrospective review of routine HMIS data	Not routinely researched	99% decline in cases and admissions, 97% decline in cases	2000-3	No	Yes	No	Before	Not deployed	Before	Attributable to mass deployment of ACT and IRS
Rwanda ⁸⁶	Retrospective review of routine HMIS data + Household surveys	Not routinely researched	72% decline in confirmed cases, 47% decline in malaria deaths	2006-2010	Yes	Yes	No	Before	Before	Not deployed	Scale-up in ITN and ACT coverage

Table 2 Findings for Pubmed-indexed publications of RDT products evaluated in Ghana

Product	Comparator	Main findings	Authors' conclusions	Reference
Partec®	PCR	Sensitivity - 62.2% Specificity - 96.0%	Partec® can be an alternative to microscopy.	Nkrumah et al 2010 ⁸⁷
Partec®	Microscopy	Sensitivity - 100% Specificity - 97.4%	Both RDTs can be an alternative to microscopy	Nkrumah et al 2011 ⁸⁸
Binax Now®		Sensitivity - 97.2% Specificity - 93.6%		
DiaMed OptiMal-IT®	Microscopy	Sensitivity (Pregnant women) - 50.5% Sensitivity (Under-5 children) - 87.7% Specificity (Pregnant women) - 82.5% Specificity (Under-5 children) - 89.6%	DiaMed OptiMal-IT® tests should not replace microscopy in our endemic setting	Ayeh-Kumi et al 2011 ⁸⁹
CareStart®	Microscopy	Sensitivity - 100.0% Specificity - 73.0%	CareStart® can be an alternative to microscopy	Baiden et al 2012 ⁹⁰

The ‘FIND reports’ have become a reference point for the performance of different mRDTs. It has led to improvements in the quality and comparability of published mRDT evaluation studies.²⁹

A Cochrane Database review of mRDT evaluation studies conducted in early 2010 identified 74 studies. Average sensitivities and specificities were found to be 94.8% (93.1% to 96.1%) and 95.2% (93.2% to 96.7%) respectively. The review concluded that the sensitivity and specificity of most mRDTs were such that they could be used to extend access to diagnostic confirmation in the management of uncomplicated *P. falciparum* malaria in sub-Saharan Africa.⁴⁹ The findings from this review corroborated those from earlier reviews.^{50, 51} and bolstered confidence that currently-available RDTs could be as accurate as smear microscopy. There is currently very little dispute about the fact that there are many mRDTs that meet acceptable performance standards at high levels of parasitemia.⁴⁹

There are however concerns about *hrp* gene deletions in a certain proportion of the population and lower multiplicity of infections as malaria control improves. Both of which could result in false negative tests. The next generation of RDTs which are currently in development will aim to target different antigens.⁵²

A PubMed search with combinations of the terms “rapid test”, “malaria” and “Ghana” conducted in February 2013 yielded four studies that evaluated the performance of different brands of mRDTs under controlled conditions. The summary of evidence supports the position that there are currently available mRDTs whose performance meets internationally acceptable standards and which can be relied upon to make clinical decision. However the poor sensitivity of DiaMed OptiMal-IT® in pregnant women (50.5%) compared to (87.5%) in children under 5 years gives cause for caution that the performances of mRDTs could vary according to the population in which it is used. (Table 2)

Implications for malaria control in Ghana

Ensuring supply of quality-assured mRDTs

While accurate mRDTs can be procured and used in clinical care, there remain concerns about the frequency of false-positive results produced by mRDTs that detect histidine-rich protein-2 antigen (HRP2-based mRDTs). This antigen is produced by the malaria parasite but persists in the blood long after the parasite has been destroyed. The persistence of HRP-2 in the blood gives rise to false-positive mRDTs results which, in the absence of careful clinical assessment, could distort the clinical picture and lead to a diagnosis of malaria at the expense of identifying the underlying cause of the illness.

Another challenge is the possibility of false-negative results due to low levels of parasitaemia. A false-negative mRDT result could cause delay in the initiation of treatment. In children, this could lead to severe malaria, with possible disability or death.³⁹ In a move to address this problem, WHO has recently adjusted the panel detection score in its program of RDT evaluation from 50% to 75% for *P. falciparum* in areas of high transmission.⁵³ This move further raises the standards required of commercially-produced RDTs.

At present there is no local production of mRDTs in Ghana. As such all the RDTs that are used in the country are imported. Those that the Ministry of Health in Ghana imports are pre-qualified by the WHO and guaranteed to be of good quality. However the liberal trading regime in Ghana means that mRDTs enter the country through other sources and may not be monitored. It is important for regulatory authorities to be alert to the high possibility that sub-standard mRDTs could be imported into the country and into clinical use.⁵⁴ Currently, there are proposals at WHO for the development of kits that clinicians can use to check the quality of mRDTs at point-of-care.^{55, 56} Until these become available however, clinicians and health facilities will still need to be careful about the brands of mRDTs that they procure for use in clinical care.

Ensuring health workers adhere to mRDT results and restrict to only positive cases

A major factor affecting effective implementation of health interventions in sub-Saharan Africa is the attitude of health workers. Inadequate health-worker performance is a very widespread problem and experience has shown that adherence to clinical guidelines is often low.⁵⁷ The cost-effectiveness of implementing test-based management of malaria hinges on health workers adhering to test-results and restricting ACTs to test-positive cases while looking for other causes of fever in the test-negative cases.

The concern that health workers may not adhere to test-results is largely founded on the use of smear microscopy in clinical care in the past. Many clinicians and other health workers in malaria-endemic countries treat patients with antimalarials even after receiving negative parasitological test results.⁵⁸ The rate at which clinicians across sub-Saharan Africa have ignored negative test results and prescribed antimalarial have ranged from 50% to 90%.^{59, 60 58}

Emerging evidence suggests, however, that once clinicians gain confidence with the use of test-based management and find a correlation between the results of the test and clinical outcome, adherence to test-results improves.

In Senegal test-based management of malaria using RDT was incorporated into national policy in September 2007. In the first year following implementation, the RDT-positive rate lagged well behind ACT consumption and this was attributed to health worker non-adherence to test results. By mid-2008 however, the RDT-positive rate and ACT consumption had nearly equalled. This corresponding use in mRDT and ACT was sustained through the rest of 2008, and throughout 2009.⁶¹

A similar observation has been made in a study in Kenya where text-message reminders were used to improve ACT malaria case management practices. Immediately after the introduction of the intervention, a 23.7% improvement in adherence was reported. This increased to 24.5% 6 months later.⁶² These observations suggest that health worker non-adherence to mRDT results may be short-lived and improve over time.

Ensuring effective management of non-malaria fevers

Closely related to health worker adherence to test results is ensuring that health workers are able to effectively manage the alternative diagnosis. The introduction of test-based management of malaria will lead to a significant increase in the number of non-malarial febrile illnesses. A challenge that this poses is how clinicians can appropriately manage this group of illnesses.^{4,63}

The many years of over-diagnosis and over-emphasis on malaria have been at the expense of attention to non-malarial febrile illnesses. As a result, the capacity for their diagnosis and management remain poorly developed. While the introduction of mRDT will improve the diagnosis of malaria, and more clearly delineate the burden of non-malarial febrile illnesses, it will not lead to improvement in the knowledge of the aetiology of non-malarial febrile illnesses. In the absence of appropriate diagnostic tools therefore, health workers are likely to either overlook negative malaria test results and still prescribe antimalarials (non-adherence) or presumptively administer antibiotics to all cases of non-malarial febrile illnesses. Essentially, clinicians will be substituting the blinded use of ACTs (in the presumptive approach) with the blinded use of antibiotics.⁶³

Self-terminating viral infections are a common cause of fevers in malaria-endemic countries, particularly under-five children. Their management does not require the use of antibiotics. However it will be extremely challenging to ask a primary care health worker in a rural area to deny patients both antimalarials and anti-

biotics, particularly when the condition has not been confirmed to be of non-bacterial origin.⁶⁴ In Cameroun, the difficulty health workers encountered with the management of non-malarial illnesses was evident in delayed appropriate treatment for children with these conditions.⁶⁵

Evidence is emerging on the potential for test-based management of malaria to lead to increased inappropriate use of antibiotics in malaria-endemic countries in sub-Saharan Africa. In Zanzibar the introduction of RDT led to an increase in the prescription of antibiotics from 27% to 37%.⁶⁶ This phenomenon has been similarly reported of studies in other parts of sub-Saharan Africa.

These increases in antibiotic use are considered to be due to the presumptive use of antibiotics to treat non-malarial febrile illnesses.⁶⁷⁻⁶⁹ Improvement in the management of non-malarial febrile illnesses should be considered integral to the process of shifting from presumptive to test-based management of malaria. An important implication of the implementation of test-based management of malaria is the need to ensure that it does not lead to irrational use of antibiotics.

If the shift to test-based management of malaria is to lead to improvement in the management of non-malarial febrile illnesses in under-five children, then mRDTs must be introduced into the health system as an integral part of the management of tropical fevers, and not just the management of malaria alone.^{64,70} This is particularly important in the case under-five children, since the recommended approach to the management of fevers in this age group is clearly-defined within the Integrated Management of Childhood Illnesses (IMCI) which has for many years promoted the presumptive approach to malaria treatment.^{7,71,72}

In Ghana, the Family Health Division of the health service develops the overarching guidelines for the management of under-five febrile illnesses. Although within the Ghana Health Service (GHS), this division is separate from the National Malaria Control Program (NMCP). Revisions to the malaria treatment guidelines alone do not guarantee application in under-five children unless it is matched by corresponding revision in the IMCI guidelines.

Nurturing and sustaining patient acceptability

The implementation of test-based management of malaria places additional responsibility on clinicians regarding the education of patients, particularly the parents or guardians (caregivers) of under-five children living in areas where presumptive treatment was practiced for many years.⁷³⁻⁷⁵ There are three important

aspects of the revised approach that caregivers may possibly react to. These are the failure to prescribe ACTs in all cases of childhood fevers, the drawing of blood to perform the tests in primary care settings, and the increased cost of care in some places due to introduction of RDTs.

In Ghana, the likely attitude of health workers towards the shift to test-based management of malaria has been assessed in a survey among 3047 caregivers of under 5 children in the Brong Ahafo region. Nearly all (98%) caregiver reported a preference for the test-based approach. The major factor that promoted acceptability included the perception that a blood test at the health centre level represented improvement in the quality of care, and was likely to lead to improved treatment outcomes.⁷⁶

The success or otherwise of the implementation of test-based management of malaria in Ghana will depend on how it leads to improved treatment outcomes for both malaria and non-malarial febrile illnesses, and how it impacts on the epidemiology of malaria in the country. There is thus now a need for improved malaria surveillance, improved diagnosis and management of non-malarial febrile illnesses and continued collaboration between clinicians, epidemiologists and program managers.

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