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Challenges of malaria diagnosis in clinical settings and disease surveillance under reduced malaria burden in Tanzania

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ABSTRACT

Febrile illnesses that are caused by malaria and other infectious diseases are a major cause of morbidity and mortality in sub-Saharan Africa. In malaria endemic countries, malaria is considered as one of the most serious febrile illnesses. Over the last two decades, major investment in malaria control has witnessed a major achievement in decline of malaria burden, however, other causes of febrile illnesses have remained prevalent. The decline in malaria burden poses challenges for the diagnosis of malaria in clinical settings, research and disease surveillance. This review highlights the challenges facing the diagnosis of malarial and non-malarial fevers under reduced malaria burden from the perspectives of parasite diagnosis and interpretations of the diagnoses of malarial and non-malarial fevers, and the possible approaches to address the challenges for a better understanding of the dynamics of febrile illnesses under reduced malaria burden.

1. Introduction

Since ancient times, fever (raised core body temperature), has had been linked with ill health. Over the past 150 years, fever wasshown to be part of the human immune response to infectious and non-infectious pyrogens, mediated by pro-inflammatory molecules called cytokines, under the homeostatic guidance of the hypothalamus in the central nervous system. Since time immemorial, the fever syndrome was connected to malaria; thus malaria has been described as a febrile illness characterized by fever and other constitutional symptoms[1]. Malaria mosquito-borne infectious disease is widespread in the tropical and sub-tropical regions, including parts of the Americas, Asia, and Africa[2]. The causative agent of malaria is a protozoan parasite of the genus *Plasmodium*, with four main human species, namely, *Plasmodium falciparum*, *Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*; a fifth species, *Plasmodium knowlesi* that infects monkeys has recently been found to infect humans in Southeast Asia[3,4]. All the clinical features of malaria are caused by the erythrocytic schizogony in the blood; thus rupture of mature erythrocytic schizonts releases certain factors and "putative" toxins (such as red cell membrane lipid, glycosylphosphatidylinositol anchor of a parasite membrane protein), which could directly induce the release of cytokines such as tumor necrosis factor and interleukin-1 from macrophages, resulting in chills and high grade fever[1]. Malaria is not a simple disease of fever, chills and rigors; in fact, malaria can present with such protean and dramatic manifestations that malaria may have to be considered as a differential diagnosis for almost all febrile clinical conditions, particularly in malaria endemic areas.

2. Changing malaria epidemiology

Available data show a decline in malaria in endemic areas of sub-Saharan Africa, including Tanzania. Thus, between 2000 and 2015, the number of new malaria cases fell by 37% globally and by 42% in Africa; in the same period, malaria mortality rates fell by 60% globally and by 66% in the African Region[5]. The decline in malaria incidence and mortality was largely due to the use of the highly effective malaria interventions of artemisinin-based combination therapies (ACTs) and long lasting insecticidal nets (LLINs). In the particular case of Tanzania, there is evidence that malaria burden has declined so that the overall prevalence of malaria in under-fives dropped from 18.1% in 2008 to 9.7% in 2012 representing a relative

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reduction of 46.5% in the prevalence of malaria among under-fives in the country[6,7]. Though there is a decline in the proportion of fevers attributable to malaria[8], clients still attend to health facilities on account of febrile illnesses due to non-malarial causes[9]. Thus, data from Northeastern and Southeastern Tanzania indicate that despite the recorded decline in malaria infection prevalence which should plausibly translate into a reduction in fever cases, fever prevalence has remained high both from the facility[10,11] and community[12,13] based data. This shows that febrile illnesses are still highly prevalent in Tanzania despite the reported decline in malaria and that, unlike in the past when malaria was highly endemic, non-malarial causes have taken precedence as the main causes of febrile illnesses[14,15]. The decline in malaria burden poses challenges for the diagnosis of malaria from the perspectives of parasite diagnosis and interpretations of the diagnoses of malarial and non-malarial fevers by prescribers and clients in clinical settings and disease surveillance[16].

3. Challenges related to parasite diagnosis in clinical settings, research and disease surveillance

The diagnosis of malaria has had difficulties both from the clinical and laboratory viewpoints, a situation made worse with the changing malaria epidemiology. About two decades ago when malaria was highly endemic and before the adoption of the comparatively expensive antimalarial drugs of ACTs, malaria diagnosis was based on a syndromic approach whereby all patients with fever were presumptively treated with an antimalarial drug[17]. At that time, this was justifiable for the following reasons: firstly, although fever is not specific for malaria, it has the advantage of being highly sensitive[18] and though treatable, malaria is a potentially fatal disease, hence sensitivity becomes more important than specificity[19]. Secondly, because of high endemicity, a high proportion of patients with fever have parasitaemia that may not necessarily be responsible for the febrile illness[20,21], such that presumptive treatment with cheap first-line antimalarial drugs (chloroquine, amodiaquine and sulfadoxine-pyrimethamine) was cost-effective[22]. Thirdly, it was because of the unavailability of reliable laboratory support for malaria diagnosis, particularly in peripheral health facilities that handle the biggest burden of febr-ile illnesses. This prompted the development of algorithms such as the one used in the integrated management of childhood illnesses (IMCI) strategy in an attempt to improve the syndromic case management of malaria[23]. By then, in highly malaria endemic areas, when laboratory support was not available, patients with any level of parasitaemia would receive an antimalarial drug, even if other causes of fever are present. Although when using the IMCI algorithm, it was shown that 70% of patients clinically classified to receive an antimalarial treatment had detectable parasitaemia[18], it was difficult to associate the presence of malaria parasites with the febrile condition because of the non-specificity of fever in febrile illness conditions, which makes fever to be not a good sign for malarial illness in holoendemic settings[24]. While in clinical settings, a positive malaria rapid diagnostic test (mRDT) or microscopic parasitaemia of any level would be the accepted criteria for prescribing an antimalarial drug, the situation will be different in epidemiological research settings. Thus, in research settings such as in assessing the effectiveness of interventions, this would require specific cut-off values of parasite count for a case definition of malaria depending on the season, fever prevalence and pyrogenic threshold of parasitaemia for malarial illness in different epidemiological settings[25]. The mere presence of malaria parasites may not necessarily mean that the fever is due to the plasmodial infection; the fever could be attributable to other causes as well[21].

Presumptively treating all febrile illnesses as malaria leads to massive injudicious use of antimalarial drugs. For example, in a study done in Northeastern Tanzania, microscopic blood examination data showed that more than half of patients receiving antimalarial treatment at government hospitals did not actually have malaria parasitaemia[26]. Similar findings were demonstrated by studies examining the rate of injudicious purchase of antimalarial drugs from the informal private sector[27]. Though the introduction of mRDT was envisaged to reduce the syndrome-based case management of malaria by making them universally available so that only mRDT positive cases are treated with an antimalarial drug[28], after ruling out malaria in the absence of diagnostic capacity to identify the actual cause of the febrile condition[29], prescribers often find themselves in a challenge to make a clinical decision and consequently resort to the syndrome-based guidelines to give an empiric treatment[30,31]. Despite the national roll-out of mRDT in line with the World Health Organization (WHO) recommendation of universal parasitological testing before treatment as a strategy to reduce overtreatment with antimalarial drugs[32], overtreatment has remained to be a problem because of inconsistencies in diagnostic capacity. Recent WHO data show an increased rate of diagnostic testing in public facilities in the African Region[5], however, the situation is different in the private sector where people seek malaria treatment from retail drug stores, where testing is rarely done[33,34]. In some situations, over-the-counter antimalarial drugs were shown to be the most popular first choice in the management of acute febrile illnesses among children and adults[35]. Stock out of mRDT has also been cited as a reason for not testing[36-38]. However, even when RDTs are available, they may not be universally used and instead prescribers revert to presumptive treatment when patient workload was high or during staff shortages[36].

Although microscopy is a useful tool for malaria diagnosis, its detection limit is relatively high. For the standard Giemsa-stained thick blood films, the detection threshold has been estimated to be 5–20 parasites/μL; however, under field conditions, a threshold of about 50–100 parasites/μL blood is more realistic but can still be higher in remote settings with less skilled microscopists and poor equipment[39]. A number of factors such as sample collection, processing, microscopic examination of the blood smear and equipment, as well as the malaria incidence and prevalence need to be considered as they may limit the detection level of $\geqslant$ 100 parasites/μL of blood[39]. This implies that microscopy might miss lower density infections both in endemic and low transmission settings. It has been shown that in areas where malaria prevalence is below 10% as measured by nucleic acid tests (NATs) such as the PCR, the majority (88%) of the infections cannot be detected by expert microscopy[40]. Such submicroscopic parasitaemia contributes substantially to malaria transmission[41,42], and although their attribution to a febrile illness has not been well characterized, such a possibility exists[43,44]. The contribution of submicroscopic infections to malaria transmission and febrile illness is likely to increase with declining malaria burden as a result of lowered naturally acquired immunity to malaria[45]. The role of submicroscopic infections in lowering hemoglobin levels has also been documented[46,47]. Cases of malarial illnesses due to submicroscopic parasitaemia are likely to be few, but they may be missed by routine microscopy and may be considered to be non-malarial, therefore receiving inappropriate treatment is likely to prolong the illness.

The diagnosis of malaria becomes even more problematic as malaria endemicity declines, because it becomes more difficult to associate parasitaemia with a malarial illness in an individual and as a public health problem such as in disease surveillance[21]. This is because a decline in malaria infection (parasitaemia) prevalence would

plausibly translate into a reduction in proportion of fevers attributable to malaria parasitaemia, conceivably changing the diagnostic accuracy of malarial disease from the clinical and parasitological viewpoints as changes in malaria infection prevalence would also change the diagnostic performance (sensitivity, specificity and predictive values) of the clinical and parasitological diagnoses[48]. Clearly as malaria endemicity changes from high to low intensity of transmission, parasite diagnosis becomes difficult because the currently available mRDT such as the histidine rich protein (HRP)-2 based mRDT may fail to detect low levels of parasitaemia because of low sensitivity[49]. The mRDTs, in particular the HRP-2-based tests, are highly sensitive for *Plasmodium falciparum* infections above 100–200 parasites/μL, but presently do not reliably detect lower-density parasitaemia. This has also been demonstrated in Zanzibar islands of the United Republic of Tanzania along the Indian Ocean coast which has reached an elimination setting where it was shown that the sensitivity of the HRP-2 based mRDT was low as a result of the decline in malaria prevalence[50].

Thus, as malaria transmission declines throughout the world, accurate diagnosis becomes increasingly important both for individual case management and disease surveillance[51]. It is now obvious that, under elimination settings (low transmission) the routine parasitological tests of malaria, namely, microscopy and mRDT would face a number of drawbacks as demonstrated by NATs in low malaria transmission settings, when it was shown that a high proportion of individuals had low-level malaria parasitaemia that was not detected by microscopy or mRDT, revealing a high proportion of asymptomatic infected individuals[49]. This finding suggests that there is a possibility that microscopy and mRDT may be of limited utility for monitoring disease or parasite prevalence in some elimination settings, hence the need for more sensitive tests of which the NATs have consistently been shown to be superior to mRDT and microscopy in detecting infections at levels below the detection limits of a competent microscopist[50]. As countries progress towards malaria elimination, the need to detect submicroscopic infections becomes increasingly important, because infected persons serve as reservoirs of malaria infection and may sustain transmission without clinical illness. Therefore, it will be necessary to incorporate more sensitive NATs into elimination programmes for use at point of care and in surveillance[51].

4. Challenges from the prescribers' perspectives

Countries in sub-Saharan Africa, including Tanzania that are endemic for malaria experience some degree of seasonality in malaria transmission based on rainfall pattern. The proportion of fevers due to malarial illness will rise during high transmission and fall in the low transmission seasons. Similarly, the proportion of fevers due to malarial disease will decrease as malaria infection prevalence declines to levels of elimination settings[51], while the non-malarial causes of febrile illnesses continue to be the main causes of attendance to health facilities[14,15].

A reduction in the proportion of cases of febrile illnesses positive for malaria as a result of malaria decline may have varied implications regarding utility of mRDTs for malaria case management. First is the possible misconception that negative test results are false-negative results, which would reduce trust and confidence in the tests[52]. Prescribers face challenges in the diagnosis and treatment of febrile illnesses because a presumptive clinical diagnosis of malaria based on the fever symptom and sign is not sufficient for giving the right treatment. While laboratory testing by microscopy or mRDT helps in making a clinical decision to prescribe an antimalarial drug for positive cases, it really becomes a dilemma to make a clinical decision for negative cases because of the limited diagnostic capacity for non-malarial causes of febrile illnesses[53].

Out of the uncertainties on the aetiologic agents of non-malarial fevers, prescribers may resort to presumptive diagnosis and treatment of febrile cases based on their training in IMCI[54] as shown in Northeastern Tanzania[55]. In the study in Northeastern Tanzania, it was shown that of the 162 under-fives who received an antimalarial drug prescription, less than a quarter (21.6%) had positive mRDT results, implying that contrary to policy guidelines, more than three quarters (78.4%) received an antimalarial drug prescription despite having negative mRDT results[28]. Although the rollout of mRDTs for routine use in all levels of healthcare was envisaged to be a strategy for targeting antimalarial use to only those with positive mRDT results[32], the finding from Northeastern Tanzania showed an alarming rate (more than three quarters) of over-treatment with antimalarial drugs. The reasons commonly given are a lack of trust in the accuracy of the mRDTs, fear of the consequences of missing a true malaria case, mind set on previous WHO and IMCI strategy recommendations, clients pressure to get an antimalarial drug prescription, and uncertainty about how to manage the other causes of fever. Studies among clients also report a lack of trust in mRDTs accuracy because it is qualitative, which is enhanced by conflicting advice from different health facilities where microscopy and count of parasites are more reliable. Clients also lose trust to mRDTs results as they feel better after taking antimalarial drugs even if the mRDT is negative conceivably due to self-limiting disease conditions.

Furthermore, a high prevalence of non-malarial causes of febrile illnesses has the potential of discouraging laboratory testing for malaria, which could result in missed malaria cases. Failure to identify the non-malarial causes of febrile illnesses has the potential for the overprescription of antibiotics out of fear of missing bacterial causes of febrile illnesses as shown in Northeastern Tanzania[55]. Findings from Northeastern Tanzania showed that, almost all (93.0%) of the patients with negative mRDT results received an antibiotic prescription on suspicion of invasive bacterial diseases, probably representing an overprescription of antibiotics because even in areas of low to moderate malaria transmission, invasive bacterial disease is not common in under-fives with non-severe illness[56]. Giving an antibiotic prescription to all febrile under-fives with a negative mRDT result is not justifiable because recently it has been shown that most under-fives with fever probably have a viral disease that does not require an antibiotic[15]. Thus, it is worth investing in improving diagnostic tests and training for other causes of severe and non-severe febrile illnesses in malaria elimination settings so as to make accurate testing and reporting of malarial and non-malarial febrile illnesses[51,57].

5. Challenges from clients' perspectives

A reduction in the proportion of cases of febrile illnesses positive for malaria as a result of malaria decline may have varied implications regarding clients' adherence to the management of non-malarial fevers[13]. As malarial fevers decline, clients would continue to attend to health facilities on account of fever due to non-malarial causes[15]. Quite often, patients may be dissatisfied to be told they have no malaria while they have constitutional symptoms that they link with malaria[58], and they would rather seek for antimalarial drugs even if they have been diagnosed to have a non-malarial fever, hence continuous public education that not all fevers are due to malaria is needed[13]. In most instances, clients are very familiar with the biomedical constitutional signs and symptoms such as fever, body pain and weakness which are not specific for malaria

and they do not relate the signs and symptoms to the presence of malaria parasites as the cause of true malarial disease[59]. Clients seem to have construed that by being referred to the laboratory for malaria testing, the mRDT can identify any cause of ill health and as such enable the prescriber to make the appropriate diagnosis and treatment; therefore, even if the mRDT is negative, meaning the illness is not due to malaria, the mRDT should also be able to identify the alternative causes of the illness and they should be told what are they suffering from and get a treatment for that[59].

Our experiences show that clients' judge parasitological testing based on mRDT as being not very accurate for malaria diagnosis because it is qualitative; and that examination made microscopically on a blood slide with counting of the number of parasites is more accurate. Thus, they will often ask "how many parasites do I have, in Swahili, nina maleria mangapi" as they believe that this shows whether one has few or many parasites that would reflect on illness severity. Traditionally, patients have equated fever (hot body) to malarial illness[60]; thus when laboratory findings show no malaria, clients get disappointed and may opt to consult another laboratory, because quite often the reason for demanding a laboratory test for malaria is to get the assurance that the fever is due to malaria and thus a justification to take an antimalarial drug. Most community members in malaria endemic countries, including Tanzania lack the correct knowledge about the causes of febrile illnesses and most have the notion that fever and malaria are synonymous and quite often used interchangeably[30,54]; therefore even at a time that malaria has remarkably declined, malaria is still perceived to be a much more common cause of fever[12,13,61,62]. Due to lack of knowledge, most clients expect a positive malaria test and when given negative results, sometimes they may not accept them and would put pressure on the prescriber to consider a diagnosis of malaria[63], and if the prescriber do not concur they may resort to self-medication with antimalarial drugs[64,65].

The demand for laboratory testing dates back to the time when malaria was highly endemic, thus in the holoendemic Kibaha District, Pwani Region of Tanzania[60], caregivers of under-fives were asked whether they thought laboratory tests were necessary in the management of childhood illnesses, and the reasons for needing laboratory testing when the large majority reported that they needed laboratory testing in order to ascertain the diagnosis (98.3%) and get correct treatment (89.4%); and close to two thirds (61.2%) could cite lack of correct diagnosis and treatment as the reasons for a poor treatment outcome. Misdiagnoses can lead to clients' dissatisfaction and a negative response to health interventions as it might well be in the malaria elimination settings if clients judge that the non-malarial fevers are due to misdiagnosis of actual malarial illness if they are not told what they are suffering from in the face of being negative for malaria by mRDT[59].

The scale up of the malaria interventions of LLINs and ACTs use has clearly demonstrated a major gain in the decline of malaria infection prevalence[8], which should have plausibly translated into a reduction of febrile illnesses by the reduction of the malaria attributable fevers. However, febrile illnesses have continued to be a major cause of attendance to health facilities[11]; and recently it has been shown that there is a high prevalence of treatable aetiologic agents of the non-malarial fevers[66]. Since fever has traditionally been equated with malarial illness[58], community members might conceive that the malaria interventions of LLINs and ACTs are partially effective[12], which might negatively affect their decisions to continue using the interventions in the pre-elimination phase. Clearly, uncertainties on the effectiveness of interventions have negative consequences on their sustained use, which is really crucial to be addressed in the consolidation phase towards malaria elimination[12]. Thus, there will be an increasing demand for highly sensitive and specific laboratory tests for malarial and non-malarial causes of fevers in malaria elimination settings.

To individuals and communities, as they assume the sick role when they have a febrile illness, their expectation is that their sickness, whether malarial or non-malarial illness, will be sorted out at the health facility[59] and that their role would be to adhere to the prescribed regimen in order to get cured. Misdiagnosis and therefore mistreatment due to unavailability or poor diagnostic services both for malarial and non-malarial illnesses have the potential of making individuals and communities lose trust to the malaria interventions that have been shown to be effective and thus serve as a barrier to their sustained use by making the interventions not attractive even for those who would get high benefits (those with malaria or at risk of getting malaria) from them. Individuals and communities learn over time about the effectiveness of malaria interventions from the outcomes of past users, thus misdiagnosis and mistreatment may affect sustained uptake in two ways: first, misdiagnosis scales down the expected benefits of uptake, since even if the interventions were fully effective, individuals would only realize the benefits if they were correctly diagnosed and really had the disease[67]. Second, uptake of malaria interventions depends on a learning process in which the motivation to use shows variability based on unobserved factors that vary unpredictably within and between individuals over time depending on disease status. The motivation to use the malaria interventions relies crucially on disease status (presence or absence); thus those who actually have malarial illness will be highly motivated to use the interventions, while those without malarial illness may have a low or even a negative motivation. Misdiagnosis and therefore mistreatment of febrile patients culminates to inefficient use of resources, more prolonging their ill health, so that those who were treated inappropriately because of incorrect diagnoses may be worse off than if they had not been treated, thus emphasizing on the need for accurate diagnosis and treatment of both malarial and non-malarial febrile illnesses[67].

Furthermore, in addition to these immediate negative effects, misdiagnosis and therefore mistreatment can have a negative effect on information transfer regarding effectiveness of the intervention because communities continue to suffer from fevers due to non-malaria causes and thus they may rate the interventions of LLINs and ACTs as being ineffective, which will make the interventions not appealing even to those who truly have malaria or are at risk of getting malaria and would still get high benefits from the use of the interventions. Perceived efficacy and effectiveness are central to acceptability and uptake of interventions, thus, in the absence of appropriate diagnosis for both malarial and non-malarial fevers, individuals and communities are likely to lose trust on the currently available malaria interventions such as the LLINs and ACTs that have been shown to work, thus serving as barrier for their continued use in the malaria elimination phase[12].

6. Possible approaches to address the challenges

Strengthening the capacity of the health system for the diagnosis of malaria and the alternative causes of febrile illnesses is of paramount importance. Since time immemorial, the diagnosis of malaria has had difficulties because of the reliance on the fever syndrome as the entry point in the clinical algorithms for malaria diagnosis[68,69]. The situation is likely to be more worse when malaria transmission and prevalence are progressively reduced because clients would continue to attend to health facilities on account of non-malarial causes of febrile illnesses[70]. While the adoption of mRDTs has significantly reduced the syndromic management of malaria, the mRDTs may not be sensitive and robust enough to detect low level and asymptomatic infections as malaria declines to low endemicity[41], hence the need to invest in the more robust and sensitive tests such as the NATs[51]. The NATs depend on the PCR, which is the most accurate method

for the diagnosis of malaria parasites but this requires expensive equipment and reagents, highly trained laboratory personnel, and has long turnaround time. As malaria prevalence declines, transmission also declines to levels whereby infections become asymptomatic; such infections are estimated to be the source of 20%–50% of all human-to-mosquito transmission[42]. Diagnosing asymptomatic cases of malaria is challenging because asymptomatic people do not seek care and asymptomatic cases are often undetectable by microscopy or RDTs.

The changing malaria epidemiology and increased importance of surveillance in malaria elimination settings which is characterized by asymptomatic malaria infections require highly sensitive and robust diagnostic tools that can detect asymptomatic infections in the community by mass screening at low costs and fast turnaround results[71]. The loop-mediated isothermal amplification (LAMP), is a promising new NAT. Like PCR, LAMP amplifies a specific section of DNA, but does not require a thermocycler, as the reaction takes place at a steady temperature. This process uses multiple different primers and a DNA polymerase to create a stem-loop structure of DNA, which serves as a template for amplification. LAMP has a sensitivity (92.7%) similar to PCR at low parasite density (10 parasites/μL)[71]. LAMP has lower costs, faster turnaround time with high-throughput, and less technical requirements compared to PCR for malaria diagnosis; moreover, it can detect malaria DNA from dried blood spots on filter paper, which is commonly used in mass screening and treatment during community surveillance in malaria elimination settings[72].

For the diagnostic tests for malarial causes of fever to be useful to the needy majority, they must conform to the ASSURED criteria for ideal rapid diagnostic tests developed by the WHO[73]. The tests thus must be affordable by those at risk of infection, sensitive (few false-negative results), specific (few false-positive results), user-friendly (simple to perform by persons with little training), rapid and robust, equipment-free and deliverable at the point of care to the needy majority in low resources settings[74,75]. Tests with similar qualities need to be developed for the detection of non-malarial causes of fever so as to improve the management of febrile illnesses[76,77]. The use of microfluidic paper-based analytical devices is an example of such efforts[78-81]. The use of paper-based diagnostics is a potential starting point for making ASSURED diagnostic tests for both malarial and non-malarial causes of fever at the point of care[82-84].

Co-infection with multiple pathogens is phenomenon in non-malarial febrile illnesses[66], and once malaria has been ruled out, a trial and error approach is used to test one disease at a time sequentially so as to arrive at a probable diagnosis; while this may be slow, the patient's condition may also deteriorate. Such an approach may also become prohibitively expensive in low-resource settings as the cost of individual tests for each suspected pathogen will be prohibitively high. The development of low-cost, multiplex rapid diagnostic tests that can identify multiple pathogens as the alternative causes of non-malarial fevers is highly welcome. Typical microfluidic paper-based analytical devices have shown the potential for multiplexing[85] and can be used for designing multiplex tests for the prevalent treatable causes of non-malarial febrile illnesses in low-resource countries including Tanzania where co-morbidities of malarial and non-malarial fevers are prevalent[85,86].

7. Conclusion

This review has unfolded the inevitable challenges that would face in malaria endemic countries, including Tanzania, aiming towards elimination and ultimately eradication of malaria. The challenges emanate from inherent difficulties in the diagnosis and management of malarial and non-malarial fevers. To address these challenges, such countries need to make major investments in further research on diagnostics for both malarial and non-malarial causes of fever, and also the best ways to sustain the recorded decline in malaria burden so as to curtail further transmission and upsurge of malaria. This would require a sustained commitment from the policy makers in the central government, local communities, civil society, and the scientific community.

Conflict of interest statement

I declare that I have no conflict of interest.

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