

Misdiagnosis of non-malaria febrile infectious diseases as malaria in Nigeria: consequences and priority actions

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Fever means a body temperature that is above normal. It is the most common symptom people seeking health care present with at health facilities. There are many etiologies of fever but the most common is infection (viral, bacterial, fungal or protozoan) and malaria is the most commonly incriminated in tropical countries including Nigeria. This is due to the endemicity of the disease in these regions, yet 'endemicity' is not synonymous with 'will have malaria'. Malaria keep being over diagnosed in fever cases in these regions while other etiologies of fever are being overlooked and un-investigated resulting in poor patient outcome amongst other public health issues such as antimalarial resistance and patient mismanagement. Other non-malaria infectious diseases commonly misdiagnosed as malaria include bacterial sepsis, arbovirus infection, otitis media in children and so on. Studies have revealed that a lot of febrile patients are being misdiagnosed as having malaria and are being treated with an antimalarial drug they do not need. Factors responsible for this misdiagnosis include lack of awareness/bias, lack of fever management policy, human resource for health challenge and outdated/cumbersome diagnostic tools. Consequences of misdiagnosis include resistance to expensively researched antimalarial drugs, economic loss, prolonged suffering of patient, risk of death and risk of epidemic outbreak. The way out includes awareness that all fever cases are not malaria, implementation of fever management policy, research to establish other etiologies of fever in Nigeria other than malaria, testing for other etiologies of fever alongside malaria and use of better diagnostic tools for fever diagnosis.

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Introduction

Fever is the most common complaints people seeking healthcare present with in low-income, middle-income and developing countries like Nigeria [1] [2]. Fever often has

A wide range of potential causes that signal various tropical infectious diseases with high case fatality rates, yet specific etiologies are not known. In developing countries where diagnostic facilities are limited, acute febrile illnesses are frequently and dangerously misdiagnosed as malaria, this leaves the

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Actual cause of fever untreated, wastes malaria treatment and gives room for the development of resistance to antimalarial drugs as reported in [3]. Although fever is a normal response of the body to a variety of conditions, its most common cause all over the world is infection [4]. Infections may be bacterial, viral, fungal or protozoan. A great proportion of infectious diseases have fever as one of their clinical symptoms, this makes the diagnosis of febrile illnesses technical. Globally, common examples of infectious diseases with symptoms of fever include Dengue, Hepatitis A, Hepatitis B, African Trypanosomiasis, Influenza, Leishmaniasis, Measles, Meningitis, Pneumonia, Rotavirus, Schistosomiasis, Strep Throat, Tuberculosis, Typhoid fever, Yellow fever, Lassa fever and several others [5] [6]. A study was carried out between 2008 and 2010 in Cambodia by the World Health Organization Western Pacific Regional Office (WHO/AFRO), to investigate the causes of non-malarial febrile illnesses in rural areas of Cambodia and Lao PDR [3]. The study involved 1,193 febrile patients, and only about 47% had malaria (*P. falciparum* and *P. vivax*) as the cause of their fever (using highly sensitive malaria diagnosis methods- molecular inclusive). About 26.8% had their etiology unknown while the remaining 26% had etiologies other than malaria such as *Leptospira* spp. (9.5%), Dengue virus (5.4%), Influenza virus A (5.9%), *O. tsutsugamushi* (3.7%), Influenza virus B (1.8%), *Rickettsia* spp. (0.2%) and bacterial from blood culture (*Salmonella* spp., *E. coli*, *S. pneumoniae*, *E. cloacea*) (0.8%) as reported in [3]. In a Prospective Cohort Study carried out in Northern Tanzania in 2013, 870 patients with fever who were sufficiently ill to require hospitalization were examined in order to identify the actual cause of fever other than malaria. The clinical diagnosis for admission in 528 (60.7%) of the 870 patients was malaria but only 14 (1.6%) had malaria as their actual cause of fever. Deeper and more thorough diagnostic screening and procedures revealed that bacterial, mycobacterial and fungal bloodstream infections accounted for 85 (9.8%) of the 540, 14 (1.6%) of the 540 and 25 (2.9%) of the 540 was the actual cause of fever respectively. This study revealed that malaria (in contrast to the initial diagnosis and reason for admission) is uncommon and over diagnosed while invasive infections such as bacterial zoonoses and arbovirus infections though highly prevalent were overlooked [7]. In Nigeria, various attempts have also been made to study the etiologies of non-malaria fever cases, but little success has been made. The best that have been

Achieved is to confirm that all fever cases are not malaria but then the actual etiologies of these febrile cases have been poorly researched, poorly identified and poorly documented. The major challenges of this research include limited diagnostic tools, limited diagnostic skills and poorly sensitive diagnostic methods. In the Niger-Delta region of Nigeria, [8] conducted a study that confirmed that only 54.74% of febrile cases in children were actually malaria while the remaining 45.26% was non-malarial febrile illnesses. UTI (8.4%), Otitis media (7.9%), pharyngitis (5.8%) and positive bacterial culture (12.6%) were observed in the malaria negative febrile children. In a study by [9] in Sokoto, 800 febrile children that were presumptively diagnosed of malaria were examined, only 56% was confirmed to have malaria while the remaining 44% were misdiagnosed to have malaria and treated for malaria which they did not have. In another study carried out by [10] in Borno state, of 310 fever cases studied, less than 1% were positive for malaria only, 3.7% tested positive for typhoid only, while in addition to malaria, 76.8% cases tested positive for more than one arbovirus infection and about 48% tested positive for malaria and a single arbovirus infection. This reveals that though malaria may be prevalent in fever cases, malaria alone is not responsible for fever but in combination with other etiologies in a single or multiple infection. In the Bornu febrile study, malaria in combination with single and multiple arboviral infections was highly prevalent which are rarely investigated routinely in fever cases.

Factors responsible for misdiagnosis of fever

The endemicity and prevalence of malaria in Nigeria as well as other tropical countries have made fever to be commonly presumptively diagnosed and first managed as malaria. 'Endemic' however is not synonymous with 'will have malaria'. Laboratory diagnosis remains the only proven way to differentiate specifically which etiology is responsible for a particular fever. Health workers however become too familiar with malaria and continue to associate fever to malaria making 'fever' to be almost synonymously used as 'malaria'. Other febrile infections that are most often misdiagnosed as malaria include Typhoid, Chikungunya, West Nile virus, Tuberculosis, Pneumonia, Meningitis, Ebola, Hepatitis, Lassa Fever, Dengue fever, *H. pylori* infection, STIs and Yellow Fever all of which have

Similar signs and symptoms as malaria [3] [7]. Awareness of 'over' and misdiagnosis of malaria in fever cases have prompted developed countries with sophisticated and modern tools such as molecular biotechnology tools to embark on studies to unravel the actual etiologies of fever other than malaria in their regions. In the review of the scourge of malaria in Nigeria by [11], the study highlighted seven major obstacles against the eradication of malaria, two of his highlighted challenges are clinical and laboratory diagnosis inadequacies. His claims however are not just applicable to malaria but also applicable to non-malaria fever cases as well as every other diagnosable disease because proper medical laboratory diagnosis of these diseases is indeed sequel to appropriate and effective treatment and management. Examples of factors responsible for these diagnoses' inadequacies or misdiagnosis include;

01. Lack of defined national algorithm to guide from the national level how fever cases and febrile conditions should be managed.
02. Lack of a defined national and local quality control and quality assurance system that serve as a check for practices at health facilities on approaches for managing febrile cases.
03. Lack of well-defined operating standards and procedures to guide stepwise management of febrile cases (e.g reagents and preparation quality).
04. Lack of sufficient diagnostic tools and equipment necessary to make proper, specific and precise diagnosis. An average laboratory in Nigeria is only equipped to carry out a few numbers of diagnostic tests thus will carry out tests that are within the scope of what its equipped to do increasing chances of misdiagnosis and underdiagnosis.
05. WHO recommend a maximum of 40 slides per day to be viewed by just one microscopist for malaria blood film microscopy result to be validated as genuine but some health facilities have their personnel attend to as many as 70 and 100/ 8hrs shift! thus increasing chances of misdiagnosis.
06. Sharp practices and lack of integrity also accounts for a high number of misdiagnosis of febrile condition as malaria. Justifying a patient's concern for seeking medical attention with a reason, appears to be more important than unraveling a patient's actual health

Challenge.

Consequences of Misdiagnosis of fever

According to the study conducted by [12], medical misdiagnosis is the cause for almost one quarter of fatal illnesses. The effects and consequences of misdiagnosis of etiologies of febrile illnesses especially in young children can be very grievous. A medical misdiagnosed febrile condition can lead to a worsening of a patient's condition such as undue stress; anxiety; wasted time, money, tests and therapies for the patient and ultimately death. A study by [13] conducted among 2357 febrile patients in Afghanistan emphasized the fact that malaria is being wrongly over diagnosed in fever cases. In Nigeria, [14] studied 457 febrile patients that sought malaria treatment and obtained an antimalarial drug, only 3.9% tested positive to malaria. These studies revealed that more than 90% of patients are treated with a malaria drug they do not need; their actual etiologies were missed and not treated or delayed in being treated, money was wasted on the initial wrong treatment of malaria, more money wasted on the latter treatment of actual cause of fever, suffering time of patient from fever illness gets lengthened, risk of death or other injuries from actual etiology of fever and chances of resistance to expensive malaria drugs are increased as well as other possible side effects from taking an unneeded medication etc. Fever among critically ill adults has an incidence of over 75% as reported in [15], and in children, fever is the most common clinical symptoms suggesting a healthcare attention, all of which can signal (both in adult and children) any of the five leading cause of morbidity and mortality in Nigeria which are malaria, HIV/AIDS, Influenza & Pneumonia, Diarrheal diseases and Tuberculosis [16]. Fever which could be malaria or respiratory tract infection (RTI) followed by diarrheal diseases are the most common indication for admission of children in Nigeria and the four most common cause of death were severe or complicated malaria, sepsis, diarrheal diseases and RTIs. Right diagnosis remains one of the major keys to the prompt and effective management of any febrile condition and the medical condition it signals. Conversely, misdiagnosis of febrile conditions as malaria contribute to chances of increase in mortality or morbidity due to the actual etiology of the infectious disease which could be any of the top killer diseases

(Mostly infectious diseases) in Nigeria.

Priority Actions for improvement in fever Diagnosis

Research has revealed that while non-communicable and lifestyle diseases are the top causes of morbidity and mortality in developed (high- income) countries, in contrast, many of the top killer diseases in developing countries including Nigeria, Sub-Sahara Africa and Africa are communicable infectious diseases which are preventable and treatable given adequate health systems and resources as reported in [17]. Diagnosis is a key component of an effective and efficient health system which involves the process of determining the actual cause of an infection, disease or disorder. In the management of fever, it is important to establish that all fever cases are not malaria. This starts with

- Detailed history of patient such as recent medication, recent immunization, diet, family illnesses, recent travels, past surgeries, occupational hazards, sick or risk factor contacts, animal or insect bites/sting, immunocompromised? Etc
- Vital signs of patient should be observed and noted such as: looking sick, rashes, pulse rate, blood pressure, temperature, visible wound, inflammation, swellings, heamorrhage etc.
- Detailed history in combination with vital signs gives a good guide on types of laboratory tests to be recommended, also radiological and imaging test all which are useful tools used to draw facts for specific differential diagnosis of an ailment [18] [19].

The government have a role to play to address this epidemic towards prevention, detection and response to potential spread of infectious diseases. Areas of focus include;

01. Establishment of a guideline or protocol for the requirement that governs the quality of personnel at health care facilities and the quality of service rendered;
02. Allocation of resources to quality research from which national algorithms for management of different illness including febrile condition rather than leaving it to the discretion of management of individual establishment;
03. Establishment of functional health sector quality control system that monitors and evaluate the

Compliance and integrity of health facilities to established recommended health intervention policies and ethically approved methods of practice respectively.

04. Provision of requisite diagnostic tools, methods, human resource and skills necessary to improve the health of the public with a resultant life longevity and healthy society.

Next generation Sequencing - a promising approach for better diagnostics

The field of malaria diagnosis continues to benefit from extensive research towards improving the effectiveness and efficacy of diagnostic methods. One of the new diagnostic products is the malaria system microapp, a mobile device based malaria diagnostic tool that offers opportunity to test for malaria on the go. This device is considered as a low cost and automated diagnostic tool for malaria. An outcome of a proof of concept for the device revealed an accuracy of 91% as reported in [20]. A collection of other promising approaches for better malaria diagnosis and their performance is available in a study by [21]. A promising nucleic acid identification approach is Metagenomics which is the study of genetic material(s) recovered directly from environmental sample. This approach using next generation sequencing (NGS) will improve the diagnosis of febrile infections. Microbial genome extracted from febrile patient samples can be analyzed using NGS, obtained sequences can then be analyzed using Bioinformatics (BLAST), infectious etiology or etiologies of fever will be obtained. And in addition to identification of etiologies of infection, novel information of gene sequence such as antibiotics resistance genes can also be detected, and this can better guide management of fever cases with specific sensitive drugs (concise case management). With even smaller, mobile sequencers (oxford Nano-pore device), diagnosis and real time analysis can be done.

Recommendations

The consequences from non-malaria febrile diseases that are wrongly diagnosed as malaria especially in areas where malaria intervention programmes are well implemented like Nigeria can hold a community down in ways that are immeasurable or quantifiable, thus;

01. Awareness- there is a pressing need for healthcare professionals to understand the clear-cut consequence of misdiagnosis of fever for malaria;
02. Research- there is a need for research studies to establish all possible common etiologies that can be responsible for febrile conditions in Nigeria;
03. Broad spectrum diagnostic tool- there is need to scale up laboratory procedures been carried out at health facilities that can screen effectively other etiologies of fever other than malaria and typhoid tests; broad spectrum diagnostic tools that can screen samples from fever cases and detect at once all etiologies in the sample such as molecular biotechnology tool (Microarray, Multiplex PCR and the most recent Metagenomics- NGS) can be modeled to develop easy and simple to use devices such Oxford nanopore device, RDTs so as to better improve fever diagnosis.
04. Fever management policy- algorithms at national levels as well as local levels need to be established for the concise and effective management of non-malaria febrile illnesses especially in low-income/developing countries as have been developed for other ailment featuring in global health challenge such as diarrhea and pneumonia

Conclusion

There is need to begin to call and treat our fever cases as what it exactly is which can only be achieved by knowing there are many etiologies that can cause fever, searching for those etiologies alongside malaria and having the best of diagnostic tools to find them out. Diagnosis is the active responsibility of every health care personnel but chiefly Scientists; Researchers; Malariologists need to work more aggressively on developing tools, skills and methods that are easy to use. This will help provide a more precise diagnosis method to confirm actual etiologies of febrile cases especially in tropical countries like Nigeria. A strong research to study etiologies of fever common to specific regions and locations need to be carried out as well as proper awareness and behavioural change communication (BCC) to improve the culture of clinical management of fever cases and most importantly, Government need to arise to the need to establish clear cut pattern of line of treatment and management of febrile condition with the

Chances of reducing morbidity and mortality as well as fatalities that could result from misdiagnosis and consequently mismanagement

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