Prevalence of malaria among clinically malaria suspected acute febrile patients in zeway health center, Ethiopia

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PREVALENCE OF MALARIA AMONG CLINICALLY MALARIA SUSPECTED ACUTE FEBRILE PATIENTS IN ZEWAY HEALTH CENTER, ETHIOPIA

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Summary: Malaria diagnosis is a common challenge in developing countries with limited diagnostic services. The common febrile illnesses were assessed from 280 malaria suspected patients and each case was subjected to clinical and laboratory examination of malaria, relapsing fever, typhoid fever, typhus and brucellosis. Data was entered and analyzed using Epi-info version 3.1 software. Malaria accounted for 17 % (CI: 12.6% to 21.4%) of febrile illnesses. The remaining was associated with typhoid fever (18.5%; CI: 13.95% to 23.05%), typhus (17.8%; CI: 13.32% to 22.28%), brucellosis (1%; CI:-0.17% to 2.17%); relapsing fever (2%; CI: 0.36% to 3.64%) and unknown fever cause (44%). About 7% Coinfections were recorded, of which 2% treated as monoinfection. About 1.4 % non-malarial patients received antimalarial treatment. Sensitivity and specificity of Carestart Pf/pan RDTs compared to microscopy were 100% and 91%, respectively with positive and negative predictive values of 94% and 100%, respectively. The PPV of each malaria symptoms compared to microscopy were very low than the combined symptoms: fever 17%, sweating 30%, headache 18%, general body ache 22% and loss of appetite 21%. The study findings revealed high proportion of non malarial illness clinically categorized as malaria cases. Relying on parasite based diagnosis is recommended to manage malarial and non malarial cases.

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INTRODUCTION

Malaria has been widely prevalent throughout the human history (1). It causes 247(152-387) million infections and 881(610-1212) thousand deaths in the world every year (2). About 91% of the deaths and 86% of the cases occur in Africa (2). The burden of the disease generally has declined with scaling up of prevention, diagnosis and treatment coverage (3). According to world health 2010 report, the number of cases of malaria rose from 233 million in 2000 to 244 million in 2005 but decreased to 225 million in 2009. The number of deaths due to malaria is estimated to have decreased from 985 000 in 2000 to 781 000 in 2009 (2). Ethiopia is the fourth malarious countries in Africa next to Nigeria, Democratic Republic of Congo and Uganda (2). Malaria is a major public health problem in Ethiopia covering 75% of the land-mass; about 52 million (68%) of the population is at risk of acquiring infection (4). *P.falciparum* and *P. vivax* are the two dominant parasite species with relative frequency of 60-70 % and 30-40 %, respectively 4). Malaria transmition is unstable and seasonal mainly occurring from September to December followed by April to May (5).

Many malarious countries are scaling up malaria intervention programmes towards elimination which demands accurate diagnosis (6). Hence, Ethiopia set national goals of malaria strategic plan to achieve malaria elimination from specific geographical areas with historically low malaria transmission and near zero malaria death in the remaining malarious areas of the country by 2015 (4). As malaria case is declining sensitive and effective detection of parasites is crucial in order to treat patients and to control transmition of the disease (6).

Malaria control strategies require accurate diagnosis and effective patient management (7-8) as its signs and symptoms are non-specific and overlapping with other febrile illnesses (9) such as typhoid fever, typhus, relapsing fever, brucellosis etc. Overlap of clinical features and limited laboratory services in developing countries overwhelm the problems of febrile patients' management (10). Therefore, presumptive treatment of fever with antimalarial drugs as malaria remains the standard of care in many developing countries (10, 11, 12). Identification of malarial illness is found to be difficult for health professionals and community as a result of the absence of distinct symptoms and different cultural perceptions in interpretations of symptoms that results encouraging of early presentation of all fever episodes (11, 13). No clinical predictors were identified to reliably distinguish between the different infections of malaria from other febrile illness (12), because malaria symptom is the least specific of all major diseases with a range of fever from non-serious viral infection to serious, life threatening conditions. Therefore, managing febrile patient is impossible to know whether the condition is due to malaria or another disease solely on the bases of clinical presentation (14).

Most febrile illnesses are commonly associated with poverty and underdevelopment with significant morbidity and mortality (15) and these illnesses share social circumstances which are essential to their transmission and, individuals in endemic areas of the diseases are at substantial risk of contracting either concurrently or an acute infection superimposed on a chronic one (16).

In Ethiopia, microscopy and rapid diagnostic tests (RDTS) are used to diagnose malaria; however, the most frequently used diagnostic method, in all peripheral areas where a majority of malaria patients are expected to present, is based on clinical signs and symptoms (4). The magnitude of malaria and other nonmalarial illnesses from malaria suspected febrile cases and degree of confusion in malaria diagnosis and treatment were assessed to inform policy makers.

MATERIAL AND METHODS

This cross-sectional study was conducted on 280 acute febrile patients clinically suspected for malaria and attending Ziway Health Center in November 2011. The center is located in the rift valley of central Ethiopia. The study participants were those with acute fever and body temperature >37.5 or history of fever over the previous 48 hours. Patients, after their verbal consent, were examined clinically and their clinical sign and symptoms recorded. Then eligible patients who were clinically suspected as malarial cases were subjected for laboratory diagnosis for malaria (using microscopy and RDT) and febrile illnesses such as relapsing fever (using microscopy), typhoid fever, typhus and brucellosis tests using HumaTex febrile kits containing the three specific antigens.

Laboratory Diagnosis

Thick and thin blood films stained with 10% giemsa solution for 10 minutes were prepared and examined using microscopy by experienced technicians. Thick films were considered negative if no parasite (either malaria *or B. recurrentis*) was seen in at least 100 consecutive oil immersion fields.

Carestart HRP2/PLDH is a rapid, in vitro immunodiagnostic test for the detection of circulating *plasmodium falciparum Histedine Rich Protein 2 (HRP2)* and an antigen common to all four species of malaria, *pan antigen (PLDH),* in whole blood. The kit contains two specific monoclonal antibodies that have been immobilized across the test strip. The test was performed according to the manufacturer's instructions. Briefly, 5 µl of whole blood was added to a sample pad impregnated with colloidal gold-labeled antibodies to the malarial antigens. 60 µl of buffer was added into the buffer well to facilitate the flow of blood sample to the full length and the result was read at 20 min. The test is valid only if the control line is observed. The result was interpreted as *P. falciparum* infection if there is visible line on *hrp2* band, *P. falciparum* infection or a mixed infection if positive on *hrp2* and PLDH/pan band antigen marks and a mixed infection of all three or *P. vivax*, *P. ovale*, or *P. malaria* if positive on PLDH/pan antigen mark only. A limitation of this test is that it cannot speciate *P. falciparum* from mixed infections.

HumaTex febrile antigens are used to detect antibodies against typhoid fever, brucellosis and typhus. The antigen solution consists of stained bacterial suspensions which are used for screening of suspected patients by rapid slide agglutination and confirmation screen positives by serial titration on the slide. It is used for qualitative (slide agglutination) and Semi quantitative (titration) determination of antibodies against Febrile antigens in serum. The reagent contains different bacterial, vitally stained, inactivated with formaldehyde or phenol and standardized suspensions of Salmonella Serotypes (*S.typhi H, S.typhi O, S. Paratyphi AH, and S. Paratyphi BH*), *Brucella abortus* and *Proteus OX19*, named as antigen solutions.

The IgM somatic O antibody appears first and represents the initial serologic response in acute typhoid fever, while the IgG flagella H antibody usually develops more slowly but persists for longer. Two types of agglutination techniques are available: the slide test and the tube test (15). HumaTex febrile antigen reagent and serum samples were placed at room temperature and the antigen solution was mixed before use. A drop of serum was placed in six separate cells on the slide, and a drop of postive and negative control added in parallel. A drop of corresponding antigen added on the serum and spread the fluid with a disposable stick over the entire area of the cell. The slide was mixed on electric rotator for a minute and the result was read macroscopically under bright light whether agglutination was formed or not. Agglutination on *S.typhi H, S.typhi O, S. Paratyphi AH,* and *S. Paratyphi BH* cell was considered as typhoid infection, with *Proteus OX19* as typhus and with *B.abortus* as brucellosis. Titration was done for those positives in the agglutination test. The serial dilution was done by taking 100ul serum and 100ul saline solution with 1/2, 1/4, 1/8, 1/16, 1/32, 1/64 rates for each sample. The test was done in the same way as slide agglutination test employing each dilution as specimen. It was examined macroscopically for the presence/absence of agglutination within one minute rotation. Samples that showed agglutination at a dilution of 1/32 or above were considered as positive (17).

Data Analysis: Data entry and analysis was done using EPI- Info version 6 software. The prevalence of malaria, relapsing fever, typhoid, typhus and Brucellosis among febrile patients; misprescription regardless the laboratory results; sensitivity and specificity of RDT and antibody test were calculated.
Ethical Clearance: This study was conducted after getting ethical approval from the Institutional Review Board of Aklilu lemma Institute of Pathobiology, Addis Ababa University.

RESULTS

A total of 280 (63 % women and 37% men) malaria suspected acute febrile patients with mean and median age of 24 and 23 years, respectively were diagnosed for different disease etiologies. The common sign and symptoms of participants were fever (100%), sweating (56%), headache (93%), vomiting (33%), general body ache (74%) and loss of appetite (79%). Each clinical sign and symptoms compared with microscopy results showed very low predictive value positives for malaria (PPV). Accordingly fever, sweating, headache, general body ache and loss of appetite had the PPVs of 17%, 30%, 18%, 22% and 21%, respectively for malaria with respect to microscopy (Table 1). However the combinations of sign and symptoms have a better positive prediction of malaria cases (fever and sweating 31%, fever, sweating and headache 67.6% and sweating, headache, vomiting, loss of appetite and bodyache 80%).

Of the total malaria suspected patients, only 48(17%; CI: 12.6% to 21.4%) were microscopically positive for malaria. Among the positives 45% were infected with *P. falciparum* and 55% with *P. vivax*. Six (2%; CI: 0.36% to 3.64%) of febrile patents were infected with *Borella recurrentis* under microscopic examination (Figure 1). On the other hand, 51(18 %) were malaria positive with Carestart HRP2/PLDH RDTs of which 8.5% were *Pf,*51% pan positive and 40.4% Pf or pan positive) (Figure 1). The sensitivity and specificity of CareStart Pf/pan in comparison with microscopy were 100% and 91%, with Positive and Negative predictive values of 94% and 100% respectively. The distribution of malaria cases varies among different age group of malaria suspected febrile cases (Table 2). The result showed malaria cases is much higher (25%) in malaria suspected febrile children compared to non malarial febrile illnesses (typhoid, 3.3%, typhus 10% and Rf 0%).

The prevalence of other febrile illnesses was also assessed from the malaria suspected patents. Of the total febrile patients, 39% were reactive for typhoid antibody tests in the screening test (slide agglutination) of which only 18.5% (CI: 13.95% to 23.05%) were positive at confirmatory test (titration >4 folds), 32.8% were typhus antibody reactive in the slide agglutination test of which only 17.8% (CI: 13.32% to 22.28%) were positive in the confirmatory test (titration above fourfold) and 3.2% patients were reactive for brucellosis in the agglutination test and only 1% (CI: -0.17% to 2.17%) were reactive at titration (Table 2). The sensitivity, specificity, positive and negative predictive values of direct agglutination and titration above fourfold were calculated as indicated in table 3. Concurrent infections (about 7%), with more than one etiologic agent of febrile illness were recorded. Of which 1.4% of patients were concurrently infected with malaria and typhoid fever, 1.4% of patients infected with malaria and typhus, and 4.3% of patients infected with typhoid fever and typhus. From 7% coinfected cases, 2% were treated as mono infection. About 1% of malaria and typhus coinfected patients were treated as malaria only; 0.7% malaria and typhoid fever coinfected patients were treated as malaria only and 0.36% typhus and typhoid fever co-infected cases were treated as typhus only. About 1.4% non malarial patient received antimalarial treatment with negative microscopy and RDT results, one case treated as falciparum with Quartem and three treated as vivax with chloroquine.

DISCUSSION

The findings evident that, of 280 malaria suspected acute febrile patients, the prevalence of malaria was only 17% microscopically (18 % with Carestart Pf/pan malaria rapid diagnostic tests) and the rest 83% were due to other fever causing illnesses and nonmalarial undifferentiated fever. Accordingly, typhoid fever, typhus, relapsing fever and brucellosis accounted for 18.5%, 17.8%, 2% and 1%, respectively on the confirmatory test results. Seven percent (7%) were concurrently infected with more than one fever causing agents and 2% of coinfected patients received treatment as mono infection.

Similar studies conducted in 653 acute febrile patients in Northwestern Ethiopia reported malaria as a major cause of febrile illness (62%), followed by pneumonia (7%), typhoid fever (5.8%), typhus (5.1%), and Brucellosis (2.6%) (17). Compared to this findings (17) malaria has low role of causing febrile illness which could be due to the overall reduction of malaria cases in the country(4) between 2009 and 2011 and seasonal and epidemiological and seasonal differences between northern and central Ethiopia.

The hospital admission review in Australia on the etiologic agents of febrile returned travellers indicated that, only 27 % of diagnoses were malaria followed by respiratory tract infection (24%), gastroenteritis (14%), dengue fever (8%) and bacterial pneumonia (6%) (18). In India, 88% of patients with acute fever tested for malaria didn't have evidence of malaria by light microscopy or malaria RDTs (9) and similarly we found 83% non malaria acute fever cases. In another study, among non-malaria febrile cases, about 40% of the patients received anti malaria treatment, despite the negative results with rapid diagnostic tests (9) and similar results recorded in our finding even if very low (1.4%) despite of having all diagnosed febrile illnesses results and negative microscopy and RDT test.

Historically and today, a large proportion of patients with febrile illness in places where malaria is common are treated with antimalarial drugs, but without specific diagnosis (19, 20). Antibiotic prescription of febrile patients is also high (21). Federal ministry of health (22) report indicated that in a non epidemic year, from 5 - 6 million clinical malaria cases and only about 600,000 confirmed cases are reported from health facilities. The observation of fever alone, and of fever in combination with chills and/or headache, achieved quite high sensitivities, but both criteria resulted in high rates of overtreatment. Any narrower combination of symptoms resulted in sensitivities unacceptable in relation to the detection of a life threatening illness. The measurement of axillary temperature failed to achieve sufficient sensitivity or specificity to be useful (23). In this study observation of specific sign and symptoms has low prediction of malaria cases whereas the combination of symptoms achieved high malaria prediction values. Combination of sign and symptoms will have a good malaria case prediction in developing countries with less access to laboratory based examination. In Ethiopia, fewer than 20% of malaria infections are confirmed by laboratory methods and the rest relies on clinical history and examination. Clinicians almost invariably respond to positive malaria tests by prescribing antimalarial, but often respond to negative tests by ignoring them and prescribing antimalarials anyway (18). When diagnostic facilities are available, half or more of those with negative test results are still treated for malaria (19, 20). When diagnostic facilities are not present, the proportion is even higher. Overdiagnosis of malaria is substantial in the formal health-care sector throughout Africa, based on clinical symptoms alone (24).

In developing countries malaria diagnosis is mainly based on clinical grounds and treatment given without obtaining a blood test, despite the lack of accuracy of perception for detecting fever and lack of accuracy of symptoms and signs to diagnose malaria. Clinicians appeared to make malaria treatment decisions on the basis of complex mmm lines involving a mixture of conventional clinical logic and diagnostic algorithms on the one hand and social factors with no obvious basis in clinical logic on the other (24). Targeting antimalarial to those who have malaria and identifying and treating other causes of serious febrile diseases is an undisputed goal, but is far from the current state of affairs (19, 20). Clinicians need to believe in the diagnostic accuracy of rapid tests for confirming or ruling out malaria and such change could come by developing fever treatment algorisms for malaria negative patients. Although most acute febrile patients don't have malaria, they continue to receive antimalarial therapy (9).

Investigations conducted in Tanzania indicate that one of the reason clinicians frequently gave treatment was due to patient's expectation of over prescription. They also use tests to confirm their suspicions, rather than as a way to make a diagnosis or allocate treatment (24). In this study we found that 7% of patients were concurrently infected with more than one pathogenic agent, similar with the study findings conducted in Egypt, which indicates 12.4% of febrile patients with concurrent infection (25). Concurrent infections with different pathogenic agents are common in developing countries possibly due to environmental and social factors that favor the spread of the disease (25).

The findings revealed parasite based diagnosis is mandatory to declare that the patient has malaria. The findings, 83% clinical malaria do not have evidence of malaria in microscopy and RDT implies poor diagnosis continues to obstruct effective management of febrile patients while most febrile cases are assumed and treated as malaria. This is mainly due to absence of differential diagnosis, presumptive treatment of febrile cases, non-specific clinical presentation of different febrile illnesses; high prevalence of asymptomatic infections and coinfection. Almost equivalent burden of typhoid (18.5% and typhus (17.8%) with malaria (16.5%) was observed in clinically malaria suspected patients in the health center. The combination of sign and symptoms resulted high malaria positive predictive values than specific sign and symptoms. Given the lack of reliable clinical predictors, availing accurate diagnostic tests are likely to be of great clinical values. This finding can let to recommend relying on parasite based diagnosis to discriminate malarial patients. The antibody tests, especially agglutination test, using currently in the health facility are poor to distinguish the real cause of illness which implicate the need of alternative diagnostic tools.

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Conflict of interest

The author's declare that there is no competing interest

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Demographic variable & Clinical history	Number	Percentage	PPV (%)
Fever	280	100%	17%
Headache	261	93%	18%
Loss of appetite	220	79%	21%
General body ache	216	74%	22%
Sweating	156	56%	30%
Vomiting	92	33%	-
Fever and sweating	86(30%)	31%	31%
Fever, sweating and headache	189(67%)	67.6%	67.6%
Sweating, headache, vomiting, loss of appetite and body ache	224(80%)	80%	80%
Others	18	6.4%	-

Table 1: Frequency of common clinical signs and symptoms of patients with acute febrile illness (n=280)

Age (yrs)	Age 5-11	12-15	16-20	>21
Malaria	8/32 (25%)	9/33 (27%)	15/63(23%)	14/152 (9%)
Typhoid	1/30 (3.3%)	5/33(15%)	10/63(16%)	32/152(21%)
Typhus	3/30 (10%)	6/33 (18%)	17/63(27%)	26/152 (17%)
Rf cases	0	1/33(3%)	3/63(5%)	2/152 (1.3%)

Table 2: Distribution of febrile illnesses in different age categories

Screening Tests		Titration >4 fold results of typhoid, typhus and brucellosis						
		Positive	Negative	Total	Sensitivity	Specificity	PPV	NPV
Typhoid agglutination	Positive	52	57	109	100%	75%	48%	100%
	Negative	0	171	171				
	Total	52	228	280				
Typhus agglutination	Positive	50	42	92	100%	82%	54%	100%
	Negative	0	188	188				
	Total	50	230	280				
Brucellosis agglutination	Positive	3	6	9	100%	98%	33%	100%
	Negative	0	271	271				
	Total	3	277	280				

Table 3: Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV) HumaTex febrile antigens of typhoid, typhus and brucellosis tests

Figure 1 Etiology and frequency of acute febrile illnesses