Malaria and human immunodeficiency virus infection among male employees of a sugar estate in Malawi

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Abstract

In sub-saharan Africa, where malaria is endemic and diagnostic and laboratory services are limited, fever is generally presumed to be due to malaria; however, the proportion of fevers actually related to malaria is unknown in most places. This study was conducted to determine the relationship between fever, malaria parasitaemia and human immunodeficiency virus (HIV) infection. Between February and April 1994, 643 consenting adult male workers of the Sugar Corporation of Malawi (SUCOMA) in Nchalo, Chikwawa District, Malawi were enrolled in a cross-sectional study. Participants underwent routine physical examinations and data were collected on age, axillary temperature, and history of fever or other illness in the 2 weeks before enrolment. Patients with axillary temperature ≥37·5°C were considered to be febrile. Blood was collected and thick blood films were prepared and examined for the presence of malaria parasites. HIV testing was done using the Wellcozyme® enzyme-linked immunosorbent assay. Complete information was obtained from 605 subjects (94%), of whom 248 (41%) reported a history of fever (only 15% of the fever reporters were parasitaemic), 139 (23%) were HIV positive, and 131 (22%) received an antimalarial drug. HIV infection was significantly associated with fever but not with parasitaemia. Fever reporters and non-fever reporters were of similar age (means 32·8 and 33·1 years, respectively). These data suggest that in this population there was both high HIV seroprevalence and gross overestimation of fever as malaria. High HIV prevalence makes it necessary to re-examine the common practice in Malawi of treating all fever among adults as malaria.

Keywords: malaria, *Plasmodium falciparum*, human immunodeficiency virus, prevalence, Malawi

Introduction

Presumptive treatment of fever with antimalarial drugs is a common practice in sub-saharan Africa where *Plasmodium falciparum* malaria is common, and diagnostic services for malaria are limited. In most of these countries, fever is generally regarded as malaria. In Malawi, malaria or fever presumed to be due to malaria constitutes a major public health problem. In 1991, among 4309722 malaria cases reported in outpatient clinics, 61% (2641727) were persons ≥5 years of age (MALAWI, 1991).

Because of the high morbidity and mortality associated with malaria in young children, presumptive treatment of malaria is generally recommended in endemic areas (WHO, 1990). However, in adults with some level of immunity the signs and symptoms of acute, uncomplicated malaria are clinically indistinguishable from those of other common illnesses (REDD *et al.*, 1992) and malaria is less likely to be fatal. Diagnosing malaria solely on the basis of clinical presentation in such a setting is unreliable, and could expose many patients to a potentially toxic antimalarial drug such as pyrimethamine/sulfadoxine, the first-line treatment for malaria in Malawi. The extent of antimalarial drug overuse due to a wrong presumptive diagnosis influences drug budgets, and could hasten the development of drug resistance in the parasite population (WERNSDORFER & PAYNE, 1991), as well as increase the incidence of adverse reactions. In this paper, we report the prevalence of reported fever and human immunodeficiency virus (HIV) infection among adult male sugar estate workers in Malawi and the frequency of antimalarial drug use for treatment of fever presumed to be malaria. We also report the association between fever, parasitaemia and HIV infection in adult Malawians.

Subjects and Methods

This study was conducted at the Sugar Corporation of Malawi (SUCOMA) at Nchalo, Chikwawa District, in the rift valley of southern Malawi, a large rural sugar estate (60 m above sea level) approximately 50 km south of Blantyre, the commercial capital of Malawi. The average yearly temperatures on the estate range from 19·7°C to 32·7°C and the average annual rainfall is between 800 mm and 1100 mm (December to April). In this area, malaria transmission is intense throughout the year due to the presence of large and small bodies of water used for irrigation. SUCOMA employs about 5000 men, 70% of whom are between 18 and 30 years of age.

Between February and April 1994, the peak season for malaria transmission in Malawi, a convenience sample of adult men employed by SUCOMA who sought treatment from the estate health centres was asked to participate in this study; participation was voluntary. At each clinic session, study personnel explained the purpose of the study, conducted health education sessions, distributed materials used by the Ministry of Health for the prevention of HIV and other sexually transmitted diseases, and invited people to volunteer for the study. Those who volunteered to participate were then told that blood would be taken and tested for the presence of malaria parasites and HIV. If they agreed they were counselled before blood was drawn, emphasizing HIV testing procedures, the meaning of a positive or a negative test result, and the fact that HIV testing was anonymous. Post-test counselling was provided 3 months later for participants who wanted to know their test result. This session emphasized the difference between being infected with HIV and having the acquired immune deficiency syndrome (AIDS). During both counselling sessions, HIV risk reduction was discussed with participants. Consenting participants were examined by a physician and the following information was obtained: age, axillary temperature, main complaint, other complaints, history of sexually transmitted disease in the past 3 months, and type of work. Each patient was questioned about fever episodes in the 2 weeks before enrolment in the study, and the type of treatment received. Patients with enrolment axillary temperature ≥37·5°C were regarded as being febrile.

A 5 mL tube of venous blood was drawn from each patient's arm, allowed to clot, centrifuged, and the serum transferred to a vial. This sample was then tested for the presence of HIV antibodies using Behring Diagnostika™ enzyme-linked immunosorbent assay (ELISA) (Behringwerke, Frankfurt, Germany). All samples were tested twice, and only those which reacted twice were confirmed with the Wellcozyme ELISA (Wellcome, UK). A thick blood film was prepared for examination for *P. falciparum* and stained with Giemsa's stain. The parasite

density was calculated by counting the number of asexual parasites against 300 white blood cells, assuming a cell count of 6×10^9/L.

Urine samples were collected from the first 300 patients enrolled only (due to limited reagents available for urine testing) and evaluated with a test developed to identify sulphonamides (TODD *et al.*, 1992) and a modified Saker–Solomons test which identifies chloroquine, amodiaquine, quinine and proguanil (MOUNT *et al.*, 1989). Because the urine test for sulphonamides does not distinguish sulfadoxine, all positive tests were regarded as evidence of sulfadoxine ingestion.

We defined fever reporters (FR) as patients with 2 weeks' history of fever or an enrolment axillary temperature ≥37·5°C. Data entry and analysis were undertaken using Epi-Info 5 software (DEAN *et al.*, 1990). Contingency table data were analysed using the Mantel–Haenszel χ^2 or Fisher's exact test as appropriate. A value of $P<0.05$ was considered statistically significant. The study was approved by the Malawi Health Sciences Research Committee.

Results

The admission characteristics of the patients are shown in Table 1; 643 adult males aged 18 to 65 years were enrolled and 605 (94%) patients had complete information available; further analyses were restricted to these patients (Table 1); FR included 240 with a history of fever in the previous 2 weeks and 8 with enrolment axillary temperatures ≥37·5°C. Those not reporting fever ('non-fever reporters', NFR) and FR had similar mean parasite densities, and a similar percentage were parasitaemic, at enrolment (Table 1).

Table 1. Characteristics at enrolment of patients with and without reported fever; SUCOMA, Malawi, 1994

Characteristic	Fever reported Yes	No	Total
No. of patients	248 (41%)	357 (59%)	605 (100%)
Age groups (years)			
<19	10 (4%)	11 (3%)	21 (4%)
20–29	110 (44%)	127 (36%)	237 (39%)
30–39	70 (28%)	107 (30%)	177 (29%)
40–49	42 (17%)	81 (22%)	123 (20%)
≥50	16 (7%)	31 (9%)	47 (8%)
Mean age (years)	32·8±10·1	33·1±10·3	33·0±102·2
No. parasitaemic	38 (15%)	53 (15%)	91 (15%)
Mean parasite density	301/mm^3	292/mm^3	293/mm^3
Mean temperature (°C)	37·7±0·44	36·5±0·34	36·6±0·39

Twenty-two percent of enrolled patients were HIV seropositive (139/605): 27% (68/248) among FR and 20% (71/357) among NFR (Table 2). FR were significantly more likely to be HIV positive than NFR ($P<0.05$) and HIV infection was significantly associated with fever but not with parasitaemia ($P<0.05$) (Table 2). Among the 605 adult men enrolled in the study, 226 (37%) reported having been diagnosed with a disease in the 2 weeks before enrolment (Table 3). There was no difference in their distribution among FR and NFR.

Table 2. Association between reported fever, parasitaemia and human immunodeficiency virus (HIV) seropositivity; SUCOMA, Malawi, 1994

	Fever reported Yes	No	*P*
Parasitaemia			
Yes	38	53	0·95
No	210	302	–[a]
HIV positive			
Yes	68	71	0·03
No	180	286	–[a]

[a]Referent category.

Table 3. Numbers of persons reporting any disease within two weeks of enrolment; SUCOMA, Malawi, 1994

Diagnosis	
Fever/malaria	122 (54%)
Upper respiratory tract infections	29 (13%)
Sexually transmitted diseases	20 (9%)
Tuberculosis	17[a] (8%)
Diarrhoea	13 (6%)
Other	25 (11%)
Total	226 (100%)

[a]11 of the 17 self-reported tuberculosis patients were infected with HIV.

Table 4. Distribution of patients by reported antimalarial treatment type and fever status; SUCOMA, Malawi, 1994

Treatment	Fever reported Yes	No	Total
PS[a]	61 (25%)	5 (1%)	66 (11%)
Chloroquine	55 (22%)	7 (3%)	62 (10%)
Chloroquine+PS[a]	2 (1%)	1 (<1%)	3 (1%)
Analgesics only	74 (30%)	3 (1%)	77 (13%)
None	40 (16%)	319 (89%)	359 (59%)
Data not available	16 (6%)	22 (6%)	38 (6%)
Total	248 (100%)	357 (100%)	605 (100%)

[a]Pyrimethamine/sulfadoxine.

Prior ingestion of antimalarial drugs was reported by 131 of the 605 subjects (22%); of these, 101 (77%) were HIV positive, including 79 FR (78%). Five of the 30 HIV negative patients reporting drug intake (17%) were FR. This difference was statistically significant ($P<0.001$). Details are given in Table 4; 48% of FR (118) and 4% of NFR (13) reported having received antimalarial drugs. Reasons for ingestion of antimalarial drugs among the NFR could not be ascertained. Analgesics were the most commonly used medication for fever. Three percent (18) of all enrolled patients reported consulting traditional healers for treatment of their fevers; FR (17/248) were more likely than NFR (1/357) to have done so ($P<0.05$).

Of the 300 eligible patients, urine was obtained from 236 (77%). Of these, 115 (51%) were FR, 38 of whom (33%) were parasitaemic. Twenty-three (85%) of the 38 patients who reported having ingested some antimalarial drugs were still parasitaemic at enrolment, including 16 (70%) who had taken chloroquine; none reported ingesting pyrimethamine/sulfadoxine. We could not determine what other antimalarial drug had been ingested by the remaining 7 patients. Urine testing confirmed the presence of chloroquine metabolites in 9 of the 16 patients (56%). No sulphonamide was found in any of the 16 urine samples tested.

Discussion

This study showed that fever or a recent history of fever is not highly predictive of malaria in adult male patients at this sugar estate in southern Malawi. Indeed, fever was much more likely to be associated with HIV infection than with malaria parasitaemia. The prevalence of reported fever (41%) was consistent with a 1992 national survey which found that nearly 38% of adults >19 years old reported fever in the last 2 weeks (ETTLING *et al.*, 1994). The finding of an HIV seroprevalence rate of 23% was also consistent with another study on the same estate, which found an HIV seroprevalence rate of 25% (KUMWENDA, 1996). Other studies conducted among women using antenatal clinics in areas close to the study site have documented HIV

seroprevalences ranging from 17% to 32% (MALAWI, 1995).

This study found gross overtreatment as malaria of fever in adults. Of the 248 patients with a history of fever, only 15% were parasitaemic but 48% reported treatment with an antimalarial drug, suggesting that (i) fever is not a valid indicator of malaria in adults in this setting, and (ii) there was gross overtreatment of fever as malaria. Treatment of all fevers as malaria in adults has several disadvantages. First, patients are needlessly exposed to drugs with the potential to cause severe side effects; adverse reactions associated with ingestion of sulpha-based drugs have been reported among AIDS patients in the USA and Africa (GORDIN *et al.*, 1984; COLEBUNDERS *et al.*, 1987; PHILLIPS-HOWARD & WEST, 1990; BJÖRKMAN & PHILLIPS-HOWARD, 1991). The effect of sulphonamides on patients infected with HIV who have not yet progressed to AIDS is not well understood. Second, treatment of all fevers as malaria results in misdiagnosis and undertreatment of the actual condition causing the fever. Third, indiscriminate use of pyrimethamine/sulfadoxine may shorten the time it takes for the malaria parasites to develop resistance. One of the principal factors that promotes drug resistance in malaria parasites is prolonged exposure to that drug. If a smaller proportion of all the *P. falciparum* parasites in Malawi were exposed to pyrimethamine/sulfadoxine, the emergence of widespread resistance would be delayed, making it possible to prolong the time that the mixture remains effective as first-line treatment. Fourth, indiscriminate use of pyrimethamine/sulfadoxine is costly. A 1994 study which examined the cost implications of changing from a policy of presumptive diagnosis to one of microscopy-based diagnosis and treatment in an outpatient setting in Malawi found a substantial reduction (from 40% to 7%) in the number of prescriptions written and dispensed within a period of 3 weeks (JONKMAN *et al.*, 1995). This represented a saving of US$ 14000, 3% of the hospital's annual drug budget.

A significantly higher proportion of individuals with HIV infection reported fever than did HIV negative individuals. Persons with HIV infection are known to be more prone to other infections which could induce fever, and HIV is itself frequently a cause of fever. The cause of fever in such patients should be sought and appropriate treatment given.

Although we do not know if the patients in our study took their drugs as prescribed, over two-thirds (92/131) of the patients who had ingested some chloroquine continued to be parasitaemic 2 weeks later. Assuming that these patients had completed their doses of medication as recommended, this would suggest the presence of chloroquine-resistant parasites. Studies conducted in 1990 among children under 5 years of age in Mangochi (a district in southern Malawi with similar ecology to the study area) found over 80% of *P. falciparum* infections resistant to chloroquine at the RII and RIII levels (BLOLAND *et al.*, 1993). Further studies are needed to determine the level of resistance to antimalarial drugs among adults in our study area.

The combined effect of high HIV seroprevalence and overtreatment of fever as malaria makes it necessary to reconsider the current widespread practice in Malawi of treating all adults with fever as having malaria. Wherever microscopy is available, especially in big cities, screening of adults with fever should be considered before treatment for malaria is initiated. Although restricting treatment to parasitaemic individuals may delay treatment of patients with falsely negative blood films, most adult patients in this setting already have some degree of immunity, so the delay would rarely result in severe or complicated disease. Therefore, a policy of directed treatment would be safe in this population and should improve the quality of patient care by properly diagnosing and treating patients for their actual disease. Additional studies are also needed to determine the specific causes and proper management of non-malarial fevers. Such studies should aid Malawi's malaria control efforts by ensuring better management and targeting of scarce public health resources, and in prolonging the time that pyrimethamine/sulfadoxine remains effective as the first-line treatment for malaria.

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