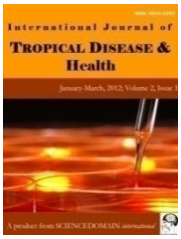

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# Bloodstream Infections and Malaria as Causes of Fever among Adult Medical Patients at a Referral Hospital in Malawi

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***Authors' contributions***

*Authors AT, JR, FN and GF conceived and designed the study. Authors AT, CM and FN coordinated the study. Author AT wrote the study proposal was responsible for documentation and analysis and wrote the first draft. Author EC was responsible for the laboratory procedures and aspects of the study at KCH. Author HSG trained and supervised the research staff and laboratory staff of KCH and was responsible for the laboratory diagnostics in Cologne, Germany. Authors FN and GF supervised the clinical aspects of the study. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background and Aims:** In Sub-Saharan Africa management of adult patients with febrile illness consists very often of empirical antibacterial and ant malarial treatment. This study examines the frequency, species identification and antibiotic susceptibility of bacterial

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isolates from blood and determines the frequency of malaria and the proportion of verified malaria cases among presumptively treated patients at a Malawian hospital.
**Study Design:** This is a cross-sectional survey.
**Place and Duration of Study:** Patients were enrolled at the Medical Department of Kamuzu Central Hospital, a referral hospital in Lilongwe, Malawi, between October 2010 and March 2011.
**Methodology:** Patients ≥18 years with an axillary temperature ≥37.5℃ were included. Blood cultures, malaria rapid diagnostic tests (RDTs), thick blood smears and HIV testing were performed.
**Results:** 180 patients (58.3% female, median age: 31 years) were enrolled. Out of 157 patients, 89 (56.7%) tested HIV positive. Bacteremia was found in 19 (10.6%) patients including 6 (31.6%) *Streptococcus pneumoniae,* 6 (31.6%) *Escherichia coli* and 5 (26.3%) *Salmonella enterica* (4 *Salmonella enterica* serotype Typhimurium and 1 *Salmonella enterica* serotype Typhi). *S.* typhimurium and *E. coli* isolates showed frequent resistance to chloramphenicol, ampicillin and cotrimoxazole. Ceftriaxone was given to 110 (61.1%) patients. Malaria was confirmed by positive smear and/or positive RDT(s) in 57 (31.7%) cases. Presumptive antimalarial treatment was administered to 120 (66.7%) patients, however only 54 (45%) of these tested malaria positive.
**Conclusion:** Empirical treatment of bloodstream infections should be based on antibiotic susceptibility of common local pathogens. Clinically suspected malaria should be confirmed by using malaria diagnostic testing before treatment. The use of malaria RDTs has to be carefully supervised and adherence to test results is advisable.

*Keywords: Fever; bacteremia; malaria; Malawi.*

## 1. INTRODUCTION

Knowledge of pathogens causing bloodstream infections and their antimicrobial susceptibility is increasingly becoming a crucial issue in Sub-Saharan Africa as bacteremia is a major reason for febrile illness and resistance to antimicrobials is increasing [1,2]. However, malaria is often the main provisional diagnosis made in febrile patients presenting to African hospitals and treatment is routinely empirical. Over-diagnosing malaria and overuse of antimalarial drugs are common practice [3,4]. This can lead to inappropriate treatment of febrile patients.

In Malawi, where malaria and HIV are endemic, bloodstream infections are progressively emerging. Particularly infections caused by non-typhoidal salmonellae are increasingly found [1]. Blood culture systems are scarce and empirical treatment of febrile illness is common. Surveys on bloodstream infections in adults in the central region were carried out in 1997/1998 [5,6] and in 2006/2007 [2]. Recently, better availability of broad spectrum antibiotics led to a widespread use of ceftriaxone. At the time we carried out our study ceftriaxone was the most common prescribed antibiotic at the Medical Department of KCH (Kamuzu Central Hospital, Lilongwe, Malawi, Unpublished data). The national guidelines for management of malaria were changed in 2007 and recommend the use of lumefantrine-artemether as first-line treatment for uncomplicated malaria [7]. Malaria and sepsis are among the three most frequent provisional diagnoses on admission for medical patients (F Agyeman-Duah et al., Kamuzu Central Hospital, Lilongwe, Malawi, Unpublished data).

The aim of this study was to determine the proportion of malaria (positive blood smear and/or positive RDT) and bloodstream infections among adult patients presenting to a

central hospital in Malawi. Furthermore, we aimed to evaluate antibiotic susceptibility of isolated pathogens to improve empirical treatment for febrile adult patients.

## 2. METHODOLOGY

### 2.1 Study Design and Setting

This cross-sectional survey took place at the Medical Department of Kamuzu Central Hospital (KCH), a government-funded tertiary care hospital in Lilongwe, Central Malawi.

Malawi has a sub-tropical climate and the wet season lasts from November to April [8]. Malaria is endemic throughout Malawi and the main parasite species causing malaria is *Plasmodium falciparum* (approximately 98% of cases). Population totals 13.1 million with an HIV prevalence of 11% among adults age 15-49 [9]. Six million cases of malaria are estimated to occur per year [10].

KCH serves the central and part of the northern region of Malawi. During daytime medical patients are triaged in the medical outpatient department (OPD). Medical admissions mostly follow self-referral to the OPD. Occasionally patients are referred from health centers, district hospitals or from within KCH. Admitted patients are sent from the OPD to the medical admission ward where further investigations and management are undertaken prior to transfer to the medical wards.

### 2.2 Participants and Study Size

Patients presenting to the medical admission ward were screened for eligibility by research assistants (trained nurse and clinical officer) between October 2010 and March 2011 from Monday to Friday during daytime. Male and female patients ≥18 years with an axillary temperature ≥37.5°C measured on admission were included in the study, after written consent was obtained. Patients were excluded if they were unable to give informed consent like comatose patients and those in need of urgent assessment. The study size was limited by time of study period and study staff availability.

### 2.3 Investigations

Patients' medical history was captured by the study staff using a structured questionnaire including questions concerning previous treatment with antimalarial drugs or antibiotics, pre-existing tuberculosis and use of bed nets.

Following skin disinfection 12 to 15 ml of blood was drawn for a single blood culture (Hemoline™, Biomérieux), full blood count (FBC), thick blood smear and the malaria rapid diagnostic test (RDT) Paracheck Pf® (Orchid Biomedical Systems, India). Eight to 10 ml of blood was inoculated into the aerobic biphasic blood culture bottle. Four ml of blood was put in an EDTA container from which the blood for the Paracheck Pf® RDT was taken. Blood culture bottles and EDTA containers were transferred to the laboratory within one hour. Blood for a second RDT (BinaxNow® Malaria RDT; Inverness Medical, USA) and HIV testing was taken by finger prick. All blood samples were taken prior to initiation of in-hospital antimicrobial treatment.

Standard operating procedures (SOPs) were available for blood drawing, identification of microorganisms, susceptibility testing of bacteria and for storing of strains in cryovials. Clinical examination was performed by the clinician on duty within the routine clinical setting. No specific documentation or SOP was applied.

## 2.4 Laboratory Methods

HIV test kits were used according to the manufacturer's instructions and following the national guidelines. First of all Determine® HIV-1/2 (Inverness Medical, Japan) was used followed by UniGold$^{TM}$ HIV (Trinity Biotech, Ireland) in case of a positive result of the Determine® HIV-1/2 test. If discordant results were seen in these two tests, SD Bioline (SD Standard Diagnostics) was performed as a third test to decide on the HIV status. The result was documented in the patient's file and/or health passport. All patients tested received pre- and post-test counseling.

Paracheck Pf® and BinaxNow® RDTs were performed following the manufacturer's instructions and the result was documented in the patients' file. The preparation of thick blood smears was done in the laboratory by using EDTA blood. Thick blood films stained with Field (Lab Tech Chemicals, Malawi) were examined for malaria parasites by oil immersion microscopy (100x objectives).

Complete blood count and differential were conducted using the FBC machine Beckman Coulter (United States).

Blood culture bottles were incubated at 36±1°C and examined macroscopically once daily for a maximum of 7 days. Turbid bottles or bottles with growth of colonies were examined by Gram stain. Subcultures onto blood agar and MacConkey agar incubated in air as well as chocolate agar incubated in $CO_2$ atmosphere were routinely done after 7 days or as soon as growth was observed. Biochemical tests were performed for species identification. Antibiotic susceptibility testing was done by disc diffusion test according to the standard of the Clinical and Laboratory Standards Institute (CLSI).

All strains were inoculated into cryovials (Microbank®, Pro-Lab Diagnostics). The cryovials were stored at -80°C and finally sent to the Institute of Medical Microbiology, Immunology and Hygiene, University of Cologne, Germany. There species identification and susceptibility testing were conducted using the Vitek system (Biomérieux) and common microbiological methods.

Clinical management of the study patients was at the discretion of the hospital staff on duty.

## 2.5 Data Management and Statistical Analysis

Data were double entered in EpiInfo software (Center for Disease Control, Atlanta, version 3.5) which was used for documentation and analysis. Descriptive statistics was used for patients with bacteremia. Fisher's exact test was performed for the comparison of *S. pneumoniae* prevalence during dry and rainy season. Frequencies of verified malaria cases and all patients treated with antimalarials or antibiotics were determined.

## 3. RESULTS AND DISCUSSION

### 3.1 Results

One hundred and eighty patients were recruited for this study; 58.3% were female. The median age was 31 years (range 18 - 90 years) and the mean axillary temperature on admission was 38.6℃ (range 37.6 - 40.7℃). Seventy patients were enrolled in the dry and 110 in the rainy season.

Upon admission the most frequently recorded provisional diagnoses were malaria in 112 (62.2%) patients, followed by sepsis in 85 (47.2%), pneumonia in 36 (20%), gastroenteritis in 13 (7.2%) and tuberculosis in 11 (6.1%). More than one admission diagnosis per patient was common. The mean length of stay was 3 days (range 1 - 14 days).

All time use of bed nets was mentioned by 75 (41.8%) patients, compared to an irregular use in 48 (26.6%) and no use at all in 57 (31.6%) patients. Antimalarial self-treatment in the two weeks prior to hospital admission was reported by 47 (26.1%) patients. Prior use of lumefantrine-artemether (LA) and preceding use of sulphadoxine-pyrimethamine (SP) were indicated by 25 (13.9%) and by 14 (7.8%) patients, respectively. Eight (4.4%) mentioned to have used quinine.

Antibiotic treatment preceding admission was indicated by 26 (14.4%) patients. The most commonly used antibiotics were amoxicillin and cotrimoxazole, which were notified by ten (5.6%) and four (2.2%), respectively. Use of ceftriaxone and metronidazole was mentioned by two (1.1%) patients each, ciprofloxacin and penicillin by one (0.6%) patient each. Use of other antibiotics was declared by one (0.6%) interviewee. Four (2.2%) patients notified an ongoing cotrimoxazole preventive therapy (CPT) and one (0.6%) mentioned to have taken CPT and doxycyclin.

Treatment for tuberculosis in the past was reported by 22 (12.2%) patients, 17 (77.3%) of whom were HIV positive.

An overview of the diagnostic procedures is depicted in Fig. 1.

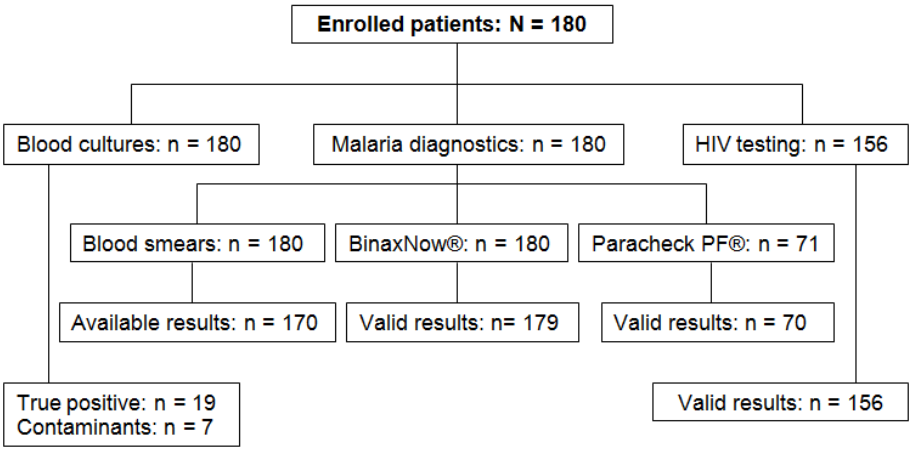


**Fig. 1. Flow diagram of diagnostics of enrolled patients**

Confirmed malaria was defined as a positive blood smear and/or positive RDT(s). Malaria was diagnosed in 57 (31.7%) cases (Fig. 2).

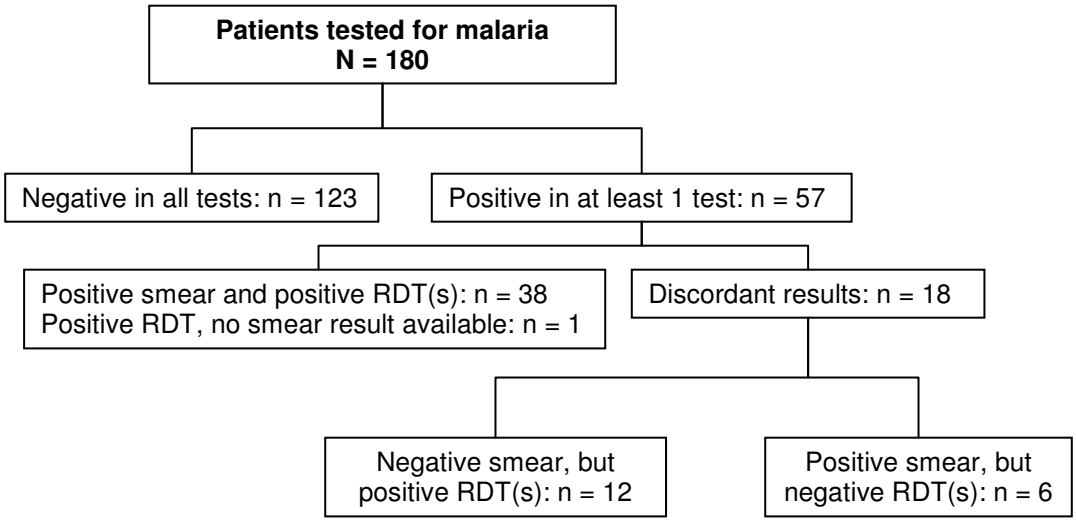


**Fig. 2. Flow diagram malaria diagnostics**

Among the 57 patients diagnosed with malaria twelve patients had reported prior use of a full course of ant malarial treatment. Seven patients took a full course of SP. Out of these, four had both a positive smear and a positive RDT, two had a negative smear but a positive RDT and one had a positive smear but a negative RDT. Five patients took a full course of LA. Out of these, two had both a positive smear and a positive RDT. Another two had a negative smear but a positive RDT. One was smear positive but tested negative in the RDT.

One hundred and twenty patients received at least one dose of antimalarials at the hospital. The most frequently used antimalarial drug was quinine. Among the 120 treated patients quinine only was given to 43 (35.8%) patients, whereas 57 (47.5%) received quinine and LA concurrently. LA only was given to 20 (16.7%) patients.

Out of the 120 presumptively treated patients, 54 (45%) had a positive malaria test. Three patients had a positive RDT result but were not treated with antimalarials during their stay. Out of these, two mentioned to have taken antimalarials prior to admission.

A total of 136 (75.6%) patients were treated with antibiotics (Table 1). Out of the treated patients, 15 (11.1%) were given a combination of two antibiotics.

**Table 1. In-hospital antibiotic treatment n (%)**

| Antibiotics | Patients N = 136 |
|---|---|
| Ceftriaxone | 110 (80.9) |
| Ciprofloxacin | 12 (8.8) |
| Penicillin | 6 (4.4) |
| Amoxicillin | 5 (3.7) |
| Cotrimoxazole | 3 (2.2) |
| Chloramphenicol | 3 (2.2) |
| Metronidazole | 2 (1.5) |
| Nalidixic acid | 2 (1.5) |
| Ampicillin | 2 (1.5) |
| Gentamicin | 1 (0.7) |
| Cotrimoxazole Preventive Therapy | 5 (3.7) |

Pathogens were isolated from blood cultures of 19 (10.6%) patients excluding samples classified as contaminated. Classical bacteria of the skin were defined as contaminants and were observed in seven (3.8%) patients.

Some features identified in the cases of patients with bacteremia are shown in Table 2.

**Table 2. Identified features in cases with bacteremia**

| Isolate | Mean age y | HIV+ n/N | Appropriate anti-microbial treatment n/N | In-hospital ant malarial treatment n/N | Diagnosis of malaria (smear and/or RDT +) n/N | Pre-hospital antimicrobial self- treatment n/N | Pre-hospital antimalarial self-treatment n/N | Outcome death n/N |
|---|---|---|---|---|---|---|---|---|
| *S. pneumoniae* (N = 6) | 36.8 | 2/5* | 4/4† | 3/6 | 0/6 | 1/6 | 3/6 | 0/5‡ |
| *E. coli* (N = 6) | 36.7 | 4/6 | 4/6 | 5/6 | 0/6 | 0/6 | 1/6 | 0/6 |
| *S.* Typhimurium (N = 4) | 28.8 | 3/3* | 4/4 | 2/4 | 1/4 | 2/4 | 2/4 | 0/4 |
| *S.* Typhi (N = 1) | 27 | nk | 1/1 | 0/1 | 0/1 | 0/1 | 0/1 | nk |
| *Pseudomonas sp.* (N = 1) | 57 | 0/1 | 0/1 | 1/1 | 1/1 | 0/1 | 1/1 | 0/1 |
| *Acinetobacter sp.*(N = 1) | 19 | nk | 0/1 | 1/1 | 0/1 | 0/1 | 1/1 | 1/1 |

**One patient not tested*
*†Two not tested for susceptibility*
*‡One outcome unknown*
*nk: not known*

*S. pneumoniae* and *E. coli* were found in six (31.6%) patients each, followed by *Salmonella enterica* serotype Typhimurium in four (21.1%) and *Salmonella enterica* serotype Typhi in one (5.2%). *Pseudomonas sp.* and *Acinetobacter sp.* were identified in one (5.2%) patient each. Two patients had both a bloodstream infection and malaria.

Three patients with bacteremia had taken antibiotics prior to hospital admission. One patient with *S. pneumoniae* took CPT, one with *Salmonella* Typhimurium used amoxicillin for six days and another one with *Salmonella* Typhimurium took an unspecified antibiotic for five days. Data for antibiotic susceptibility is summarized in Table 3.

*S. pneumoniae* was more common in the dry than in the rainy season (Fisher's Exact test, p=0.034). One hundred and fifty seven patients were tested for HIV, 89 (56.7%) of whom tested positive. Among the 19 patients with bacteremia, the HIV status was ascertained in 15 patients. Nine (60%) tested positive.

**Table 3. Number of isolates that tested susceptible in relation to the number tested n/N**

| Isolate | P | AMP | AMC | C | SXT | CI* | E | G | TE | CTX |
|---|---|---|---|---|---|---|---|---|---|---|
| **Gram-negative** | | | | | | | | | | |
| *S.* Typhimurium (N = 4) | / | 1/4 | 1/4 | 1/4 | 1/4 | 4/4 | / | 0/4 | 4/4 | 4/4 |
| *S.* Typhi (N = 1) | / | 1/1 | 1/1 | 1/1 | 1/1 | 1/1 | / | 0/1 | 1/1 | 1/1 |
| *E. coli* (N = 6) | / | 1/6 | 2/6[‡] | 0/4[†] | 1/6 | 6/6 | / | 6/6 | 2/6 | 6/6 |
| *Pseudomonas sp.* (N = 1) | / | 0/1 | 0/1 | / | 1/1 | 1/1 | / | 1/1 | 1/1 | 1/1 |
| *Acinetobacter sp.* (N = 1) | / | 0/1 | 0/1[§] | / | 0/1 | 0/1 | / | 0/1 | 0/1 | 0/1 |
| **Gram-positive** | | | | | | | | | | |
| *S. pneumoniae* (N = 4[†]) | 4/4 | / | / | 2/4 | 0/4[¶] | / | 4/4 | 0/4 | 2/4 | 4/4 |

*P=penicillin; AMP=ampicillin; AMC=amoxicillin+clavulanic acid; C=chloramphenicol; SXT=cotrimoxazole; CI=ciprofloxacin, E=erythromycin; G=gentamicin, TE=tetracycline, CTX=ceftriaxone*
**Sensitivity proven by testing nalidixic acid*
*[†]Only 4 of 6 tested*
*[‡]Two tested intermediate*
*[§]Tested intermediate*
*[¶]One tested intermediate*

## 3.2 Discussion

This study describes the prevalence of bacteremia and malaria in febrile adult patients admitted to a referral hospital in Central Malawi. The vast majority of febrile patients received treatment for malaria and bacterial infections. Quinine and ceftriaxone were usually administered without waiting for or following test results.

This practice may be justified in certain situations e.g. severe illness or unavailability of diagnostic facilities but it raises concerns when routinely applied. Interestingly, 110 of 180 patients received the broad spectrum antibiotic ceftriaxone and 120 were started on antimalarial treatment. However, only 19 were diagnosed with an invasive bacterial infection and only 57 were found to have malaria. A possible explanation may be that clinicians are eager to treat patients for both, bacterial infections and for malaria. This might be underlined by the initial diagnoses malaria and sepsis which were by far the most frequent admission diagnoses in our survey. Such a frequent use of a broad spectrum antibiotic in febrile patients might be not affordable in the long term. It might hinder clinicians from looking for the focus of infection and performing diagnostic procedures.

Bacteremia was diagnosed in 10.6% of our patients. The most common pathogens isolated were *S. pneumoniae* and *E. coli*. This matches well with the findings in adult patients of a previous study of Makoka et al. [2]. However, in Makoka et al.'s study Gram negative bacilli

were not further classified. The relative frequent finding of *E. coli* was previously described in children rather than in adults [11,12] whereas other studies detected non-typhoidal salmonellae (NTS) and *S. pneumoniae* to be the leading pathogens in adults [6,13]. Our study showed NTS to be the second most common isolated pathogens. Possible reasons could be that our study period was too short and in total only few patients showed bacteremia. Therefore the distribution of isolated pathogens of our survey might be not representative.

The most often used antibiotics prior to hospital admission were amoxicillin and cotrimoxazole to which NTS and *E. coli* were highly resistant. *S. pneumoniae* was fully susceptible to amoxicillin but highly resistant to cotrimoxazole. Resistance of non-typhoidal salmonellae to cotrimoxazole and ampicillin was already seen in Malawi in 1997 [5]. However, at that time no resistance to chloramphenicol was detected. Multidrug resistance (amoxicillin, cotrimoxazole and chloramphenicol) of NTS was noted by Gordon et al. [1] and is supported by our study. Makoka et al. [2] confirmed these findings, although their study did not specify *Salmonella spp*. The findings of multidrug resistance imply that use of antibiotics particularly in the primary health facilities should be more targeted if NTS are suspected. Ciprofloxacin might be a good alternative, as to our knowledge no resistance has been described in Malawi.

The number of observations in patients using cotrimoxazole as prophylaxis was too small to allow any conclusion on the potential effect on malaria and bloodstream infections.

Our study covered dry and rainy season. Given that our findings are based on a limited number of positive blood cultures, seasonal variation should be interpreted with caution. However, we showed a significant prevalence of *S. pneumonia*e in the dry season which is in line with Archibald et al. [5].

Contamination rates of blood cultures are not frequently published in clinical studies. In our study contamination was found in 3.8% of cases which is similar to a 4% contamination rate seen in a study conducted by Crump et al. [14]. However, contamination rates can be high as shown by Hill et al.[12] and Gordon et al.[1] who documented rates of 23.4% (204/871) and 21%, respectively. Makoka et al. [2] documented a contamination rate of 9.2%. Since use of manual culture systems is labour-intensive and time-consuming high contamination rates of blood cultures are likely to increase workload of laboratory staff and could waste expensive and rare materials. Therefore sterile blood sampling techniques should be taught to the staff on a regular basis to avoid contamination.

Adherence to results of malaria RDTs and smears was low in our survey. This is consistent with earlier findings [3,15,16] suggesting distrust in the test by the staff. In our study RDTs were conducted at the admission ward whereas the initial management of patients including antimalarial treatment was already started at the OPD. The staff on the admission ward and on the medical wards might have seen the negative RDT result stated in the patient's file but might have been reluctant to change an already started treatment. If RDTs were to be introduced, the test should be performed during the first evaluation of the patient prior to treatment initiation.

Eighteen discordant malaria test results were shown in our study. While most of these results are plausible, e.g. negative smear but still positive RDT, others are not such as positive smear but negative RDT. This finding underscores the need for internal and external quality control for RDTs and blood smears. Furthermore we observed quinine to be the most

frequently prescribed antimalarial drug. The Malawian national guidelines recommend quinine for patients with severe malaria and in pregnant women during the first trimester [7]. In our study clinicians used quinine also in other situations, potentially considering quinine the best option to treat suspected malaria. Consequently, continuous mentoring supervision of adherence to national guidelines is needed.

Our study had several limitations. Due to logistical and staff constraints we could not enroll patients admitted during night hours and weekends. The approved study protocol did not allow enrolling severely sick patients who failed to give informed consent. Also patients who gave a history of fever but were afebrile on admission were not included. All these exclusions may lead to an underestimation of both malaria and bacteremia among the patients. Second, for better acceptability of the blood draw, only one single blood culture was obtained from each study patient. Taking two or more blood culture bottles might have yielded more positive results. Therefore our result may again underestimate the proportion of bacteremia. Third, the number of patients with bacteremia appears too small to show seasonal variation of bloodstream infections. Fourth, antimicrobial and antimalarial pretreatment by study participants might have changed the frequency and pattern of malaria and bloodstream infections. Finally, a number of febrile cases could not be diagnosed based on the applied investigations. Some of these cases are likely to be caused by *Mycobacterium tuberculosis.* Mycobacterial blood culture was not included in the study, although Mycobacteria bloodstream infections should be expected in an area with high HIV prevalence as in our setting and shown in other studies [6,17].

Nonetheless, our study results define common causes of febrile illness in Malawi and show differences between the applied management and the national guidelines or diagnostic test results. Furthermore, the study led to an implementation of local guidelines on how to manage febrile patients at Kamuzu Central Hospital.

## 4. CONCLUSION

Knowledge of the prevailing pathogens and antibiotic susceptibility is necessary for empirical treatment of patients with febrile illness. Treating febrile patients non-selectively with broad spectrum antibiotics should be avoided due to limited availability of drugs and increasing costs. Furthermore, this procedure is likely to increase the occurrence of resistant strains. Therefore antibiotic susceptibility should be revised regularly to guide empirical treatment. Blood cultures and malarial RDTs should be performed where possible. Adherence to test results and national guidelines has to be monitored.

## CONSENT

Written informed consent was obtained by using both information sheets with detailed study explanations and oral explanations by the research assistants. Participants signed with their name or fingerprint if illiterate.

## ETHICAL APPROVAL

The study was approved by the National Health Sciences Research Committee (NHSRC) of Malawi and the Ethics Committee of the Medical Faculty of the University of Cologne, Germany (study number 10-087).

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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