Presentation, Aetiology and Management of Patients with Acute Febrile Illness in Outpatient Setting in Eldoret, Kenya

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A Research Thesis Submitted To The School Of Medicine In Partial Fulfillment Of The Requirements For The Award Of The Degree Of Master Of Medicine In Internal Medicine

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DECLARATION

DECLARATION BY CANDIDATE

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DEDICATION

I dedicate this thesis to my family for their unwavering support, guidance and love throughout this journey.
ABSTRACT

Background: Febrile illnesses cause significant mortality and morbidity and are a common presentation in the outpatient setting. Because hospital diagnoses in sub-Saharan Africa are often empirical and symptom-based, true causes of febrile illness are never established.

Objectives: To describe the presentation, aetiology and management of patients presenting with an acute febrile illness in an outpatient setting.

Methods: This was a cross-sectional study carried out at two sub-county hospitals in Eldoret. Consecutive patients 18 years and above presenting at the outpatient departments with tympanic temperature of 38°C and above were recruited. Demographic and clinical data were recorded and blood samples collected for complete blood count, aerobic and anaerobic blood cultures, thick blood smear for malaria parasites, malaria rapid diagnostic test, HIV test and random blood sugar. Identification and antibiotic susceptibility testing for all bacterial isolates were performed on positive cultures. Categorical variables were summarized as frequencies and percentages. Continuous variables were summarized as mean and median.

Results: From January to September 2013, 180 participants were enrolled into the study: median age 28 years (IQR 24-37); 99 (55%) male, 149 (83%) urban residents; and 4 (3%) tested positive for HIV. Most common presenting symptoms included headache 72 (18%), chills 61 (15.2%) and general body malaise 58 (14.5%). Median symptom duration was 3 days (IQR 2-4). Common clinical diagnoses made at the district hospitals were upper respiratory tract infection (URTI) with malaria in 35 (19.4%), URTI only in 32 (17.8%) and malaria only in 32 (17.8%) patients. Features of sepsis was present in 131 (72%) and 11 (6%) participants had signs of severe sepsis at presentation. Malaria was confirmed by RDT/blood slide in 42 (48.3%) participants. Of 180 blood cultures collected, 2 (1%; 95% CI: 0% - 4%) gram negative organisms were cultured; sphingomonas paucimobilis and sphingobacterium thalophilum. Antimalarials and antibiotics were prescribed to 87 (48.3%) and 167 (93%) participants respectively.

Conclusions: Patients with acute febrile illness can present with nonspecific but severe symptoms; sepsis and severe sepsis. Laboratory work up other than BS and blood culture is important in ascertaining diagnosis and assessing of severity of illness. A number of patient with acute febrile illness receive antimicrobials without definite diagnosis.

Recommendations: Triage of patients with acute febrile illnesses will assist in identifying those with severe symptoms. Ministry of Health guidelines on confirmatory diagnosis and treatment of malaria should be upheld. Additional local studies are required to establish causes of acute febrile illness in this population.
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Special thanks to my family and friends for their constant encouragement, support and love and Hassan for the constant humor and wise words.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HDH</td>
<td>Huruma District Hospital</td>
</tr>
<tr>
<td>KAIS</td>
<td>Kenya AIDS Indicator Survey</td>
</tr>
<tr>
<td>MOH</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>NST</td>
<td>Non Salmonella Typhi species</td>
</tr>
<tr>
<td>OPD</td>
<td>Outpatient Department</td>
</tr>
<tr>
<td>RDT</td>
<td>Rapid Diagnostic Test for malaria</td>
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<tr>
<td>UGDH</td>
<td>Uasin Gishu District Hospital</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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OPERATIONAL TERMS

**Fever:** We defined fever as tympanic temperature ≥ 38°C in this study.

The WHO Integrated Management of Adolescents and Adults guidelines (2009) define acute febrile illness as recent fever (within 48 hours) and axillary temperature of 37.5°C or above. We selected temperature ≥ 38°C so as to avoid diurnal variability of temperatures (37.2°C at 6AM and 37.7°C at 4PM) and variability of different mechanisms of measuring temperature (tympanic temperature is 0.8°C lower than rectal temperature) (Kasper, 2012).

**Bacteremia:** Bacteremia is the presence of viable bacteria in the circulating blood. Bacteremia may result from ordinary activities such as tooth brushing, dental and medical procedures or from infections. Bacteremia caused by ordinary activities is usually transient and does not normally cause infections. Bacteremia can be primary, as that caused by direct infection of blood by either an indwelling catheter and direct inoculation into blood or secondary bacteremia such as that caused by an infection at another site, for example pneumonia, leading to invasion of the bloodstream by bacteria. The body’s response to infection or bacteremia is an immune system response that can lead to ‘sepsis’. Sepsis defines the combination of infection and the body’s inflammatory immune system response which can be life threatening. Clinical detection of bacteremia occurs by collection of blood into a blood culture bottle and incubating it in a medium that promotes bacterial growth.

**Severity of Illness:** In our analysis we defined severity of illness based on the measurements that we included in our study. We used the defined systemic inflammatory response
syndrome (SIRS) as presence of two or more of the following; temperature >38°C, heart rate>90 beats/min, respiratory rate>20 breaths/min and white blood count >12,000 cells/ml; sepsis as presence of at least two SIRS criteria plus suspected infection and severe sepsis as sepsis plus hypotension (systolic blood pressure less than 90mmHg).
CHAPTER ONE: INTRODUCTION

1.1 Background and Significance
Febrile illnesses, which cause significant morbidity and mortality, are a common cause of hospital admissions in Africa (Olack B., 2014; Petit P. L., 1995; Reddy, 2010). Despite studies showing that bacterial and fungal infections are common in adults and children presenting with fever in Africa, there is still room for additional epidemiological data regarding these causes of fever in the region (Reddy, 2010). Most studies on causes of fever in Africa have focused on high risk groups only; the pediatric age groups and HIV infected adults (Susan, 2009) with few data on non-HIV infected adults.

Malaria is overdiagnosed as the most common cause of fever in patients presenting to hospitals with a febrile illness (Dougle, 1997; Reyburn, 2004). Recent studies have shown that the prevalence and incidence of malaria is decreasing, including in Kenya. A study by Noor et al in 2009 showed that majority of the Kenyan population resided in areas where predicted malaria rate was less than 5%, with prevalence in the Rift Valley region ranging between 0.5% and 5% (Division of Malaria Control, 2011; Noor, 2009).

Causes of febrile illness are innumerable. Overlapping and non-specific symptoms of bacterial infections and malaria, cause difficulties for healthcare workers in eliciting the primary cause of fever in patients (Remco, 2004a) and therefore, they depend on syndrome-oriented empirical approaches in treatment of these patients. This approach is associated with increased morbidity and mortality (Reddy, 2010). Many patients are diagnosed with ‘clinical’ malaria and treated first with antimalarials before antibacterial
treatment is commenced. Several studies have shown that more than half of patients who receive treatment for malaria have negative blood slides for malaria parasites (Dougle, 1997; Reyburn, 2004). A study by Reyburn et al in Tanzania showed higher mortality in malaria slide negative patients treated with antimalarials compared to patients who were malaria slide positive (6.9 vs 12.1%) (Reyburn, 2004). In addition, presence of concomitant bacterial infection with malaria parasitemia and increased predisposition of patients infected with malaria to bacterial infections has been described in several studies in the pediatric age groups (Sigauque, 2009).

The WHO and the Kenya MOH recently changed malaria treatment guidelines from presumptive treatment of malaria to treatment guided by malaria slide or rapid diagnostic tests (Ministry of Medical Services., 2009), but the lack of diagnostic microbiological testing capabilities in most health care facilities in Kenya (L. K. Archibald, and Reller, L. B. , 2001; Dougle, 1997) compels the healthcare workers to depend on empirical diagnosis of febrile patients based on clinical symptoms. It has been demonstrated that simple microbiological studies can improve initiation of treatment with the correct antibiotics in this setting (Dougle, 1997; Karen, 2010; Lutterloh, 2012).

Bacteremia is a common cause of febrile illness in Africa (Reddy, 2010). Streptococcus pneumoniae, Salmonella enterica (with non typhoidal salmonella as most common) and Escherichia Coli have been shown to be the most common causes of bacteremia in adults presenting with fever D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ...Breiman, R. F. (2010a); (D. R. Feikin, Njenga, M.K., Bigogo, G., Aura, B., Aol, G., Audi, A., ...Breiman, R. F., 2012; Reddy, 2010). However, due to unavailability of microbiological tests in most health facilities to confirm causes of
febrile illnesses, many patients are either misdiagnosed or empirically treated leading to increase in morbidity and mortality.

Empirical use of antibiotics has had adverse effects on patient outcomes and in the increasing development of antibiotic resistance. Several studies in Kenya have shown increased resistance of common organisms, for example salmonella typhi and streptococcus pneumoniae, to first-line, affordable and available antimicrobials (Groß, 2011; S. Kariuki, Muyodi, J., Mirza, B., Mwatu, W., Daniels, J. J. D., 2003; S. Kariuki, Revathi, G. Kiiru, J., Mwituria, J., Muyodi, J., ... Dougan, G., 2010; S. Kariuki, Revathi, G., Kariuki, N. Muyodi, J., Mwituria, J., Munyalo, A., ... Hart, C. A., 2005; Okeke, 2003; Oundo, 2000).

HIV infection is also a distinct risk factor for bacteremia. It has been shown that bacteremia is more prevalent and associated with worse outcomes in HIV positive individuals presenting with fever compared to HIV negative patients (Arthur, 2001; Gordon, 2002; Mayanja B. N., 2010; Reddy, 2010; Ssali, 1998). Non-typhoidal salmonella, streptococcus pneumoniae and mycobacterium tuberculosis have been shown to be the most common blood stream infections in patients with HIV in sub-Saharan Africa (Arthur, 2001; Reddy, 2010; Ssali, 1998).

1.2 Problem Statement
Febrile illnesses are a common presentation in healthcare facilities in sub-Saharan Africa. A majority of these febrile illnesses are caused by infectious diseases that can present with severe disease (sepsis) and its complications. Unfortunately, most diagnoses of these febrile illnesses are made empirically due to limited laboratory testing capacity in the
healthcare facilities leading to overdiagnosis of certain diseases (for example malaria) while under diagnosis of others (like bacterial infections). Inappropriate treatment (Berkley, 2005; Reyburn, 2004) and misdiagnosis of causes of febrile illnesses (such as occurs in empirical diagnosis) and their complications can contribute to inappropriate treatment and resultant high morbidity and mortality.

Empirical diagnosis and treatment of patients without microbiological confirmation is one of the causes leading to the increase in antibiotic resistance to affordable and available antibiotics (Hart, 1998; S. Kariuki, Muyodi, J., Mirza, B., Mwatu, W., Daniels, J. J. D., 2003; Malonza, 1997; Sosa, 2010). Consequently, leading to increased cost of treatment, morbidity and mortality. Scarcity of regional data on causes of febrile illness other than malaria to guide care providers to ensure comprehensive management of these patients (Reddy, 2010)
CHAPTER TWO: LITERATURE REVIEW

Febrile illness is a common presentation and a leading reason for admission to hospitals in Africa (Petit P. L., 1995; Reddy, 2010; Remco, 2004a) and is associated with significant mortality and morbidity. The HIV epidemic has led to increased incidence and prevalence of febrile illness.

Febrile illness and Bacteremia

There is scarcity of data on regional causes of fever and bloodstream infections (J. A. Crump, 2012; Reddy, 2010), with most African studies focusing on high risk groups; young children and HIV infected adults (Susan, 2009). Studies on causes of bloodstream infections in adult outpatient population are particularly rare. The few studies that have been done across Africa have shown that bacterial and fungal bloodstream infections are common, with a mean prevalence of 13.4% (range 8.5%-38.2%) in patients presenting with fever to hospital (Reddy, 2010). Despite these findings, there is limited availability of microbiological testing for febrile illnesses in health care facilities in Africa (L. K. Archibald, and Reller, L. B., 2001; J. A. Crump, Gove, S., Parry, C. M., 2011; Reddy, 2010; Remco, 2004a) apart from malaria testing. Therefore, health care providers depend on syndrome oriented diagnosis (based on clinical symptoms) and empirical treatment of patients presenting with fever to health facilities. This practice has been associated with poor outcomes, increased rates of complications and increased mortality (Berkley, 2005; Opoka, 2008; Reyburn, 2004)

A meta-analysis of community acquired bloodstream infections in Africa showed that the most common causes of bacteremia among adults in Africa were gram negative bacteria.
Salmonella enterica was the most commonly isolated organism, of which non typhi Salmonella species (Salmonella enteritica, typhimurium) (NTS) was most common (Reddy, 2010). This has been demonstrated in several other studies in Africa (J. A. Crump, 2012; Reddy, 2010; Remco, 2004a; Ssali, 1998; Susan, 2009). There were few studies from East Africa including three from Kenya in the meta-analysis by Reddy et al in 2010 showing that the most commonly isolated organisms in this region were streptococcus pneumoniae, salmonella enterica (with non typhoidal salmonella as most common) and Escherichia Coli (Reddy, 2010).

Recent data on causes of febrile illnesses have reported that bacterial zoonoses including rickettsiae, leptospirosis and viruses as commonly missed causes of febrile illness in the African setting. A study by Crump et al in Tanzania showed that in patients presenting with non-malarial febrile illnesses; malaria was overdiagnosed while bacterial zoonoses and arbovirus infections despite being common, were under recognized causes of fever (Crump, 2013). Additionally in Kenya, Richards et al (2010) that showed that ricketsial infections with were common in patients presenting with febrile illnesses. Lack of laboratory capabilities for diagnosis and the nonspecific symptoms of these infections make diagnosis difficult for healthcare providers and are therefore commonly missed.

Clinical presentations of febrile illnesses are usually non-specific. Most patients present to health facilities with fever without focal symptoms or signs (J. A. Crump, Gove, S., Parry, C. M., 2011) leading to difficulties in making clinical and empirical diagnoses (Remco, 2004a), for example in several studies on non typhoidal salmonella infections, fever and splenomegaly, which are also features of malaria were common in patients presenting to hospital (Gordon, 2002). Although malaria can be ruled out by a
blood slide examination or malaria rapid diagnostic tests, health care providers in resource limited settings have limited diagnostic capabilities to determine the etiology of the febrile illness in patients without malaria (J. A. Crump, Gove, S., Parry, C. M., 2011). It is common practice to empirically diagnose and treat patients presenting with fever to healthcare facilities for malaria first before antibiotic treatment despite negative tests for malaria (Bell, 2001; Dougle, 1997; Reyburn, 2004). As mentioned above, this practice has been associated with poor patient outcomes and increase in morbidity and mortality (J. A. Crump, 2012; Reyburn, 2004).

Existing data has shown that the prevalence of malaria is decreasing (Noor, 2009). Despite the change in MOH/WHO guidelines on malaria treatment promoting parasitological diagnosis before treatment of malaria and encouragement of further investigation of those with negative malaria tests (Ministry of Public Health and Sanitation and Ministry of Medical Services., 2010), most health centers are unable to follow these guidelines due to lack of laboratory support (Elbireer, 2011; Petti, 2005, 2006). Additionally, scarcity of regional data on causes of febrile illnesses and guidance on causes and management of other non malarial febrile illnesses, compounds the inability of health care workers to correctly diagnose and optimally manage non-malarial causes of febrile illnesses.
Malaria

Malaria is a leading cause of morbidity and mortality in sub-Saharan Africa including Kenya. Current evidence shows that the prevalence of malaria in Kenya is decreasing (Division of Malaria Control, 2011; Noor, 2009). It is estimated that 60-70 percent of areas in Kenya have a parasite prevalence of less than 5% (Noor, 2009). Kenya has four malaria epidemiological zones; highland epidemic prone areas, endemic areas, seasonal malaria transmission zones and low risk malaria areas. Western Kenya, where Eldoret is located, is classified as a highland epidemic zone that is characterized by seasonal transmission of malaria that occurs when climatic conditions favor vector breeding and malaria transmission (risk class 5 to less than 20 percent) (Noor, 2009).

Despite the change of malaria guidelines encouraging parasitological diagnosis by the Kenya ministry of health, studies have shown that overall malaria testing rates in health facilities are still low (Juma, 2011; Zurovac, 2008). According to the Kenya Malaria Survey, clinically diagnosed malaria accounted for 34% of outpatient visits in Kenya in 2010 (Division of Malaria Control, 2011). Additionally, various studies in Kenya have shown a high rate of anti-malarial treatment for malaria test negative febrile patients (Juma, 2011; Nyandigisi, 2011; Zurovac, 2008). For example, in studies by Juma et al 50.4% of patients aged 5 years and above were treated for malaria despite a negative malaria test result (Juma, 2011) and Zurovac et al in 2008 showed that 61.3% of patients above 5 years with negative malaria results were treated for malaria (Zurovac, 2008).

Low utilization of available diagnostics by health care workers as well as lack of supplies for performing these tests have been shown to encourage this practice leading to increased morbidity and mortality especially for patients who are treated with anti-
malarials without being investigated further for other causes of fever (Berkley, 2005; Reyburn, 2004).

**Sepsis**

Patients with acute febrile illnesses can present to hospital with severe symptoms and complications such as sepsis. Sepsis is a systemic inflammatory response secondary to an infection that can present with acute fever. Microbial invasion/bacteremia is not necessary for sepsis to occur as local inflammation/infection can also lead to a systemic inflammatory response (Kasper, 2012). Sepsis is an important cause of mortality in the developed countries. Despite a high burden of infectious diseases and resultant sepsis in the resource limited settings, there is scarcity of data on sepsis (Cheng, 2008). Several studies in Africa have shown increased mortality in patients admitted with sepsis that has been associated with poor recognition and management of this condition. A study by Jacobs et al in Uganda showed 43% mortality in patients admitted with severe sepsis and that most of these patients did not receive optimal medical management (S. T. Jacob, Moore, C. C., Banura, P., Pinkerton, R., Meya, D., Opendi, P., ... Scheld, W. M. for the Promoting Resource-limited Interventions for Sepsis Management in Uganda Study Group 2009). Although infectious diseases are one of the commonest causes of morbidity and mortality in our setting, the burden of sepsis and severe sepsis in Kenya is currently unknown.

In developed countries, sepsis management bundles and guidelines have been developed and implemented, leading to lower mortality rates; however, such strategies have not been implemented in low resource settings due to lack of resources to adequately manage
sepsis and its complications (Baelani, 2011; Cheng, 2008; S. T. Jacob, Banura, P., Baeten, J. M., Moore, C. C., Meya, D., Nakiyangi, L., … Scheld, W. M., 2012). Prospective studies have shown that early recognition and management of sepsis is associated with improved outcomes. Jacobs et al in Uganda in 2013 in a prospective intervention trial showed that patients receiving early and correct intervention for sepsis had lower mortality (26% compared to observational group at 45.7%) (S. T. Jacob, Banura, P., Baeten, J. M., Moore, C. C., Meya, D., Nakiyangi, L., … Scheld, W. M., 2012).

Improvement in morbidity and mortality in patients with sepsis not only requires adequate resources for diagnosis and management of these patients but also training and knowledge of healthcare workers to ensure early recognition and optimal management of these conditions and their complications.

**HIV and Bloodstream Infections**

The HIV epidemic in Africa has increased the burden of infectious diseases by lowering immunity and increasing susceptibility of infected individuals to infectious diseases. Non-malarial bloodstream infections and febrile illnesses are frequent in HIV-infected individuals, compared to those without HIV (D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., …Breiman, R. F., 2010a; C. F. Gilks, Ojoo, S. A.,Ojoo, J. C., Brindle, R. J., Paul, J., Batchelor, B. I., … Plummer, F. A., 1996; Gilly, 2001; Mayanja B. N., 2010; Reddy, 2010; Ssali, 1998). Bloodstream infection in HIV patients is usually associated with increased mortality and morbidity and have been shown to frequently be the cause of death in HIV infected individuals (J. A. Crump, Ramadhani, H. O., Morrissey, A. B., Msuya, L. J., Yang, L. Y., Chow, S. C., … Kinabo,

The meta-analysis by Reddy et al on community acquired bloodstream infections in Africa showed that non-typhoidal salmonella (NTS), mycobacterium tuberculosis and fungi were the most common cultured organisms in HIV positive patients presenting with febrile illness (Reddy, 2010). This was previously shown Arthur et al (2001), in a 10 year prospective cross-sectional study at Kenyatta National Hospital which reported that Mycobacterium Tuberculosis, NTS and streptococcal pneumoniae were the most common causes of bacteremia, however they found fungemia caused by Cryptococcus was uncommon (Gilly, 2001). In a recent study in rural Kenya, NTS bacteremia was found in 80% of HIV infected patients presenting with fever (Tabu, 2012) and this finding has also been demonstrated in several other studies in Kenya and Africa (D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ...Breiman, R. F., 2010a, 2010b; C. F. Gilks, Ojoo, S. A., Ojoo, J. C., Brindle, R. J., Paul, J., Batchelor, B. I., ... Plummer, F. A., 1996; Mayanja B. N., 2010; Ssali, 1998).

HIV positive patients are susceptible to invasive pneumococcal bacteremia (L. K. Archibald, McDonald, L. C., Nwanyanwu, O., Kazembe, P., Dobbie, H., Tokars, J., ...Jarvis, W. R., 2000; Arthur, 2001; D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ...Breiman, R. F., 2010a; Reddy, 2010; Ssali, 1998). In Nairobi, Gilks et al showed a higher incidence of invasive pneumococcal disease in HIV
infected women compared to those who were not HIV infected (C. F. Gilks, Ojoo, S. A., Ojoo, J. C., Brindle, R. J., Paul, J., Batchelor, B. I., ... Plummer, F. A., 1996). A most recent study by Feikin et al. also showed that pneumococcal bacteremia was 19.7 times higher in HIV infected individuals than in HIV negative individuals in rural western Kenya (D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ... Breiman, R. F., 2010a).

Mycobacterium tuberculosis bacteremia is also a common cause of fever in HIV patients admitted to hospital (L. K. Archibald, McDonald, L. C., Nwanyanwu, O., Kazembe, P., Dobbie, H., Tokars, J., ... Jarvis, W. R., 2000; Arthur, 2001; Remco, 2004a, 2004b)) as well as in outpatients attending HIV clinics due to increased risk of mycobacterium tuberculosis reactivation and dissemination due to the lowered immunity. TB presentation is commonly atypical in patients with HIV causing difficulties in diagnosis (J. A. Crump, Ramadhani, H. O., Morrissey, A. B., Saganda, W., Mwako, M. S., Yang, L., ... Bartlett, J.A., 2012) and therefore increase in mortality.

**Antibiotic Susceptibility**

Worldwide, there has been an increase in antibiotic resistance against common organisms. However there is scarcity of data on antimicrobial susceptibility from Africa (Ashley, 2011; Sosa, 2010). The few studies on antibiotic susceptibility in the region have shown increased resistance to inexpensive and available antibiotics (Ashley, 2011; Bjorn B., 2004). In Kenya, the rates of antibiotic resistance are currently unknown (Global Antibiotic Resistance Partnership-Kenya Working Group., 2011) but findings of increasing resistance have been shown from several studies on common bacterial isolates...
Indiscriminate, uncontrolled and empirical use of antibiotics due to lack of laboratory capabilities, deficient knowledge and self medication (Global Antibiotic Resistance Partnership-Kenya Working Group., 2011) are some causes implicated in development of antibiotic resistance. In turn, increasing antibiotic resistance has led to increases in mortality, morbidity and prolongation of the course of disease and its infectivity (Acar, 1997). Combined, all these factors have led to increased cost of treatment due to the need to use second line antibiotics, which are expensive and unavailable as well as prolongation of length of treatment.

In 2010, a study by Mengo et al on trends of antibiotic resistance of salmonella from 2004 to 2006 in Nairobi showed that 70% of the isolated bacteria were multi drug resistant (Mengo, 2010). This has been confirmed in several other studies showing similar increase in multidrug resistant salmonella in Kenya (S. Kariuki, Revathi, G. Kiiru, J., Mengo, D. M., Mwituria, J., Muyodi, J., ... Dougan, G., 2010; S. Kariuki, Revathi, G., Kariuki, N. Muyodi, J., Mwituria, J., Munyalo, A., ... Hart, C. A., 2005; Shapiro, 2001). Kariuki et al documented that 59% of NTS strains cultured in children in Nairobi were resistant to ampicillin, chloramphenicol and tetracycline but fully susceptible to ceftriaxone and ciprofloxacin(S. Kariuki, Revathi, G., Kariuki, N., Kiiru, J., Mwituria, J., Hart, C. A., 2006). In a separate study in 2006, Kariuki et al showed an increasing prevalence in NTS resistance from 31% in 1994 to 42% in 2006(S. Kariuki, Revathi, G., Kariuki, N. Muyodi, J., Mwituria, J., Munyalo, A., ... Hart, C. A., 2005). Multidrug resistant typhoid fever has been defined as infection caused by S. typhi strains that are resistant to all the
three first line recommended drugs; trimethoprim-sulfamethoxazole, ampicillin and chloramphenicol(Zaki, 2011). Despite these findings the Kenyan Ministry of Health guidelines list the above medications as first line treatment of salmonella infections (Ministry of Medical Services., 2009).

Streptococcus pneumonia has also shown an increase in its resistance to antibiotics. A recent study by Feikin et al in western Kenya showed that streptococcus pneumonia was the most common bacterial isolate cultured (58%) with 88% of these being resistant to trimethoprim-sulfamethoxazole. In the same study there was minimal resistance to amoxicillin (2%) and cefotaxime (2%) and all isolates were fully susceptible to levofloxacin(D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ...Breiman, R. F., 2010a). In a study by Kariuki et al in Nairobi in 2003, only 56.7% of S. pneumonia was susceptible to penicillin, 7.6% of the strain were resistant to two or more antimicrobial agents and the most effective agent was amoxicillin(S. Kariuki, Muyodi, J., Mirza, B., Mwatu, W., Daniels, J. J. D., 2003). More epidemiological data on resistance patterns of S. pneumoniae is required.

Resistant staphylococcus aureus is also a common cause of bloodstream infection but there is scanty data on this organism in Africa. A few studies performed in Kenya have shown a high prevalence of methicillin resistant staphylococcus aureus (MRSA). A study by Kesah et al in 2002 at KNH documented MRSA prevalence of 27.7%(Kesah, 2003). A most recent study in Nairobi documented an MRSA prevalence of 26.3% (Ouko, 2010).
Availability of Laboratory Services

There is lack of laboratory services needed to confirm clinical diagnoses and conduct infectious disease surveillance in Africa (Petti, 2005). Most health care facilities have only a few simple microscopic and kit based laboratory tests like HIV and malaria rapid diagnostic tests (Bates, 2006) or have none at all. In areas where laboratory services are available, lack of consumables, scarcity of trained personnel and staff shortage impact provision of quality laboratory services (L. K. Archibald, and Reller, L. B. , 2001; Petti, 2005) leading to frequent misdiagnoses, inadequate treatment and inability to determine local prevalence of diseases (Petti, 2005). Healthcare workers frequently do not utilize laboratory services for diagnosis in areas where these services are available (Juma, 2011; Zurovac, 2008) for example the study by Juma et al in 2011 showed that only 43% of febrile patients are tested for malaria at facilities with available diagnostics.

As development of antimicrobial resistance is increasingly being recognized, there is lack of infection surveillance laboratories in Kenya required to monitor resistance patterns of common organisms (Malonza, 1997; Okeke, 2003; Omari, 1997; Reddy, 2010; Shapiro, 2001). There is also lack of collection, storage and dissemination of resistance data by sentinel laboratories that perform antimicrobial susceptibility testing (Sosa, 2010). Development of empirical treatment guidelines will require local surveillance data characterizing causes of febrile illnesses and antimicrobial resistance to improve clinical care of patients presenting with fever.
CHAPTER THREE: RESEARCH QUESTIONS, OBJECTIVES AND JUSTIFICATION

3.1 Research Questions

What is the presentation, aetiology and management of patients with acute febrile illness in an outpatient setting in Eldoret?

3.2 Objectives

3.2.1 Broad Objective:

To describe the presentation, aetiology and management of patients presenting with an acute febrile illness in outpatient setting in Eldoret, Kenya

3.2.2 Specific Objectives:

1. To describe the clinical presentation (and clinical diagnosis) of patients presenting with an acute febrile illness in outpatient setting.

2. To determine the proportion of malaria and bacteremia in patients presenting with an acute febrile illness in outpatient setting.

3. To describe the management of patients presenting with acute febrile illness in outpatient setting.
3.3 Justification

Outpatients contribute to the majority of hospital consultations in Kenya. Febrile illnesses are a common cause of presentation in the outpatient hospital setting. The causes of febrile illnesses are innumerable. Unfortunately, they are not comprehensively investigated in resource limited settings. This is largely because of lack of laboratory capacity to conduct certain tests (such as complete blood count, aerobic and anaerobic blood cultures) and the costs of such tests are usually out of reach for the many indigent patients we serve. Therefore, many patients are empirically treated for an acute febrile illness leading to increased morbidity and mortality. Previous research studies in our settings have focused on high risk populations including; adult inpatients, HIV infected and pediatric groups. As a result, there is scarcity of data on the epidemiology of febrile illnesses in the outpatient population leading to development of generalized outpatient adult management guidelines that may not be region specific.

This study was aimed at describing the clinical characteristics of patients with an acute febrile illness and management in an outpatient setting as well as to determine the contribution of bacteremia and malaria as causes of febrile illnesses. Data from this study was immediately important for patient care (patient results were provided to the primary care providers) and will also be important for policy (in development of region specific clinical care guidelines and rational antimicrobial use) and in impressing the need for improved clinical management and bacteriological studies in clinical care of patients presenting with a febrile illness to hospital.
CHAPTER FOUR: METHODOLOGY

4.1 Study Design

This was a descriptive cross-sectional study to describe the clinical presentation, diagnoses, aetiology and management of patients with an acute febrile illness in outpatient setting.

4.2 Study site

The study was conducted between January and September 2013 at Uasin Gishu District Hospital (UGDH) and Huruma Sub-District Hospital (HDH) Outpatient Departments (OPD). Both UGDH and HDH are located in Eldoret.

Eldoret, the headquarters of Uasin Gishu County, is the fifth largest town in Kenya. The town has a local elevation ranging between 2100 metres above sea level at the airport and 2700 metres in nearby areas (7000–9000 feet). According to the 2009 census report, the population was 289,380. Eldoret has a cold and wet, tropical climate. The rainy season is between April and May, while in January to February the rainfall is minimal. According to the malaria transmission data, Eldoret is classified as a highland epidemic zone that is characterized by seasonal transmission of malaria which occurs when climatic conditions favor vector breeding and malaria transmission (risk class 5 to less than 20 percent) (Noor, 2009).

Uasin Gishu District Hospital (UGDH) is a county health facility serving the Eldoret East and Turbo constituencies of Uasin Gishu County. UGDH has a catchment population of 53,773 people and provides outpatient services including pediatric, adult and obstetric care. The hospital also contains several specialty clinics including ear, nose and throat
(ENT), ophthalmology and HIV clinics. The adult OPD is the primary point of entry for all adult outpatients presenting at the district hospital for medical care, where they are triaged and assessed before they are referred to other respective clinics. UGDH has an inpatient capacity of 10 beds. Adult patients are managed by clinical officers and a medical officer. The UGDH OPD attends to approximately 60,000 patients annually. In 2011, approximately 12,000 patients (adult and pediatric patients) were treated for clinical malaria. UGDH is able to provide only basic laboratory tests including HIV, testing for tuberculosis and malaria.

The Huruma Sub-district hospital is a county hospital located in Eldoret West serving the Eldoret North constituency. The hospital has a catchment population of 120,000 people and provides pediatric and adult outpatient care, obstetric and HIV care. The outpatient department (OPD) in the district hospital is the main entry point for all patients including the adult and pediatric patients who are attended to in the same department. The OPD attends to approximately 85,000 patients annually, with majority being either children or pregnant women. The district hospital does not have an inpatient service. Adult patients are attended by clinical officers stationed in the clinics and a medical officer. Huruma district hospital has only basic laboratory capabilities providing malaria, typhoid, HIV and tuberculosis testing.

4.3 Study population

Patients aged 18 years and above presenting to UGDH and HDH outpatient department with fever above 38°C (tympanic temperature) were recruited.
4.4 Sampling and recruitment

4.4.1 Inclusion criteria

1. Age 18 years and above presenting to the outpatient departments

2. Presence of fever >38°C (tympanic temperature), regardless of history of prior use of antibiotics or antimalarials.

3. Able to provide a written informed consent

4.4.2 Exclusion criteria

1. Lack or inability to provide of informed consent

We recruited all adult patients meeting the inclusion criteria above regardless of history of prior use of antibiotics or antimalarials.

The likelihood of a patient with fever presenting to a health facility having had ingested an antibiotic or antimalarial is as high as 56% (Reddy, 2010). Based on this and the results of prior studies that showed no differences in blood culture yield in patients who had previously used antibiotics (including HIV patients on co-trimoxazole for prophylaxis) and those who had not (D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ...Breiman, R. F., 2010a), we recruited all patients who reported prior use of antimalarials and/or antibiotics if they met the inclusion criteria above.
4.4.3 Sample size determination

We based the sample size calculation on objective number 2 looking at the contribution of bacteremia and malaria in patients with acute febrile illness. The estimated prevalence of malaria in Rift Valley, acute febrile illness and bacteremia were 5% (Noor, 2009), 11.2% (Bigogo, 2010) and 13.4% (Reddy, 2010) respectively.

Using the Fisher’s formula;

\[ n = \frac{Z^2_{(1-\alpha/2)}p(1-p)}{D^2} \]

where; Z is the percentile of the standard normal distribution type I error, p is the prevalence, \( D^2 \) is the margin of error (effect size) and \( \alpha \) is type I error. Setting \( Z=1.96 \), \( D^2=0.05 \), \( \alpha=0.05 \), \( p=\) infinite population.

We took into consideration the prevalence of malaria, acute febrile illness and bacteremia. We got a minimal sample size of 73 participants using the prevalence of malaria at 5%, a minimal sample size of 153 participants based on the highest prevalence of acute febrile illness in Western Kenya at 11.6% and a minimal sample size of 180 participants based on the prevalence of bacteremia at 13.4%. We therefore used the higher sample size of 180 participants for this study.

4.4 Data Collection Procedures

4.4.1 Participant Recruitment

Potential study participants were identified at the outpatient departments. All patients presenting to the outpatient departments with history of fever or self reported history of fever were screened for presence of fever \( \geq 38^0 \text{C} \).
Consecutive patients who met the inclusion criteria were recruited into the study. The patients' demographic information, clinical history, prior treatment, and past medical history was collected and recorded in a standardized data collection form (Appendix I). Clinical examination was performed on all patients, and findings were recorded. All patients were informed that an HIV test would be performed as part of the study, and those who consented to have the test performed were given pre-test counseling for HIV (and post-test counseling after results were read) and then blood was then collected for:

1. Malaria parasites (BS for MPS)
2. Malaria RDT
3. Complete blood count
4. Aerobic Blood Culture
5. Anaerobic Blood Culture
6. HIV test
7. Random Blood Sugar

### 4.5 Procedure for Blood Collection

Blood samples for all laboratory tests were collected once using an aseptic technique from the antecubital vein of the arm. After application of a tourniquet to restrict the flow of venous blood, the most prominent vein was chosen for venepuncture. The skin was wiped with 70% alcohol first, then swabbed with chlorhexidine and the skin allowed to dry for 1 minute before the clinician put on sterile gloves and used a syringe to collect blood.
Once the blood sample was collected, the needle used to collect the blood sample from the patient was removed and discarded. Then, a new sterile needle was used to inoculate 10mls of blood into the blood culture bottle after removal of the flip cap and disinfection of the septum of the culture bottles. After inoculation of blood, the protective cap was replaced.

From the remaining blood sample, 2mls were then placed into the complete blood count (CBC) EDTA vacutainer and 1 ml used for testing for HIV, RDT for malaria and random blood sugar as well as preparation of thick smear for malaria parasites.

Measurement of random blood sugar, HIV test and malaria RDT were done and reported at the district hospitals. Blood samples for blood cultures, complete blood count and thick smear for malaria parasites were taken daily to the AMPATH Reference Laboratory-Special Microbiology Laboratory for testing.

4.6 Laboratory Procedures

1. **Thick smear for malaria parasites:** A thick smear for detection of malaria parasites was prepared, stained with Giemsa and examined under power 100 oil immersion objective lens and reported as either positive or negative for malaria.

2. **Malaria Rapid Diagnostic Test (RDT):** We used Malaria pf (HRP II) / (PAN-pLDH) Antigen Detection Test Device (AZOG Inc.) for rapid diagnosis of malaria which has been approved by WHO for malaria testing. The malaria RDT uses an immunochromatographic lateral flow for antigen detection relying on the capture of dye-labeled antibodies to produce a visible band on a strip of nitro-cellulose. Two visible bands are present on the testing strip, one containing the parasite antigens and
the second one a control band. Blood from the patient is placed in the well of the malaria testing cassette and a buffer added. The mixture is then drawn up the test strip. If malaria antigens are present, the antibody will be trapped on the test line and the excess labeled antibodies trapped in the control line (and two lines are seen on the test strip) and the test is read as positive. If malaria antigens are absent, the test line will be invisible and one line (control line only) is seen and the test is read as negative.

3. **Random Blood Sugar:** Freestyle Optium Xceed (Abott) blood glucose meters was used to measure blood sugar. We measured blood sugar because diabetes is a risk factor for infection due to impaired immunity and hyperglycemia is one of the diagnostic components for sepsis.

4. **HIV test:** Determine™ (Abbott Laboratories, USA) and confirmatory Bioline™ (Standard Diagnostics, Kyonggi-do, Korea) test kits were used to test for HIV. If the results by the two tests were indeterminate, a tie breaker diagnostic assay, Uni-Gold™ Recombigen® HIV, was performed. HIV test was performed as it is one of the risk factors for bacteremia due to impaired immunity.

5. **Complete Blood Count:** A coulter analyzer was used in analyzing the specimen for total white cell count (with differentials), hemoglobin and platelet levels.

6. **Blood Cultures:**

   a. **Aerobic/Anaerobic cultures:** We used Hemoline™ Diphasic Performace culture bottles for detection of both aerobic and anaerobic organisms. These culture bottles have two culture media, a broth (casein peptone and gelatin peptone) enriched with
growth factors and an agar covering one side of the bottle. Each bottle was inoculated with 10mls of blood and incubated at 37°C and inspected daily for signs of microbial growth, presence of colonies, production of gas on the agar, appearance of turbidity or a deposit or hemolysis in the culture broth. All blood cultures were incubated for 7 days which is the recommended incubation time period for conventional blood cultures (World Health Organization., 2003). This period of culture was suitable for most common bacteria (including streptococcus pneumoniae, haemophilus influenza, salmonella typhi, Escherichia coli, Klebsiella spp) except fastidious bacteria like ricketssiae and leptospira that would require serological testing for diagnosis or brucellae that require longer blood culture incubation periods for up to 3 months.

Subcultures for the aerobic cultures were done on blood agar, McConkey and chocolate agar on all positive cultures while subcultures for the anaerobic cultures were performed on batched samples and placed in a CO2 jar ( Anaeropack) and examined every 24-48hours. Gram staining and identification of all colonies was then performed based on recommended guidelines (Clinical and Laboratory Standards Institute (CLSI). 2011; World Health Organization., 2003).

7. **Antibiotic Susceptibility Testing:** All organisms were identified and underwent antibiotic susceptibility testing using VITEK® 2 Antibiotic Susceptibility (BioMerieux Inc.) machine which is based on broth microdilution to provide identification and antibiotic susceptibility testing. The machine also contains an agar gradient method for provision of Minimum Inhibitory Concentration (MIC) for slow growing and fastidious organisms as well as extended microdilution when necessary.
Subculture, gram staining for bacteria identification and antibiotic susceptibility testing was done following the WHO Manual for the Laboratory Identification and Antimicrobial Susceptibility Testing of Bacterial Pathogens of Public Health Importance in the Developing World and CLSI guidelines Antimicrobial Susceptibility Testing of Bacterial Pathogens of Public Health Importance in the Developing World (Clinical and Laboratory Standards Institute (CLSI). 2011; World Health Organization., 2003)

4.7 Data collection and analysis

4.7.1 Data collection and management

All clinical and laboratory data collected was entered into the data collection form during recruitment. The data was then entered into an excel database, validated and later exported into STATA version 12 special edition for analysis.

4.7.2 Data Analysis

Data was analyzed using STATA version 12 special edition. Categorical variables were summarized as frequencies and the corresponding percentages. Continuous variables following Gaussian distribution were summarized as mean and the corresponding standard deviation (sd) while the continuous variables that were skewed were summarized as median and the corresponding inter quartile range (IQR). The relationship between receipt of antimalarial drugs and antibiotics prior to enrollment and after enrollment were assessed using a logistic regression model. We reported the odd ratios (OR) and the corresponding 95% confidence intervals (95% CI).
Age was categorized at ten year intervals with the lower limits being <20 and the upper limit being >60 years.

4.8 Limitations of the study

Due to cost limitations, we were unable to perform two sets of blood cultures. However, majority of published studies rely on one blood culture.

All blood cultures were incubated for 7 days which is the recommended incubation time period for conventional blood cultures. This period of culture was suitable for most common bacteria except fastidious bacteria that may have been missed like rickettsiae and leptospira which would require serological testing for diagnosis or brucellae that require longer blood culture incubation periods.

Due to unavailability and cost, we were unable to perform serological tests for rickettsiae and leptospira and other viral testing which could have further defined the causes of fever in patients in this study.

4.9 Ethical considerations

Approval to conduct this study including all study amendments was provided by the Moi University/Moi Teaching and Referral Hospital Institutional Research and Ethic Committee (IERC). The study was explained to potential study participants and a written/signed informed consent obtained before enrollment into the study. Each participant was given a unique identification number and all patient data was entered into the recruitment form and research database using this unique patient identification number. To maintain confidentiality, data collection forms contained only the unique identification number to ensure participant anonymity. The link between the unique
subject number and the participant’s identity was maintained securely. Computerized
data was accessible only by password and was stored in a password-protected computer.

The results of the clinical assessments and laboratory results were made available to the
treating clinician, the patient and the patient’s medical record as soon as the
investigations were complete. Patients who were tested for HIV received pre and post test
counseling and were informed of the results and referred for care if they tested positive.
The study participants did not incur any additional costs for their participation in the
study except for routine charges required for their care at the district hospital. All patients
received the standard care regardless of their enrollment into the study.
CHAPTER FIVE: RESULTS

5.1 Patient Recruitment

The study was conducted between January and September 2013. We recruited a total of 180 participants into the study; 177 from UGDH and 3 from HDH. The recruitment schema is represented in Figure 1.

Figure 1: Flowchart showing screening and recruitment of Patients Presenting with Acute Febrile Illness in Outpatient Setting in Eldoret, Kenya.
There were a total of 180 participants aged 18-74 years whose data were included for analysis. We screened 52 patients in Huruma District Hospital between February and March 2013 and recruited 3 patients. There were few patients meeting our inclusion criteria at the Huruma District Hospital. Demographic and clinical characteristics of participants presenting with acute febrile illness are shown in table 1.

**Table 1: Demographic Characteristics of Patients Presenting with Acute Febrile Illness in Outpatient Setting in Eldoret, Kenya.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency (N= 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>81 (45%)</td>
</tr>
<tr>
<td>Male</td>
<td>99 (55%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>20 (11%)</td>
</tr>
<tr>
<td>20-29</td>
<td>84 (47%)</td>
</tr>
<tr>
<td>30-39</td>
<td>45 (25%)</td>
</tr>
<tr>
<td>40-49</td>
<td>19 (11%)</td>
</tr>
<tr>
<td>50-59</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>112 (65%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>61 (35%)</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>149 (83%)</td>
</tr>
<tr>
<td>Rural</td>
<td>31 (11%)</td>
</tr>
</tbody>
</table>

Majority (80%) of the participants were young (aged 40 years and below). There was no statistically significant difference in age between males (28 years [IQR: 24-37]) and females (27 years [IQR: 23-36]) (p=0.364). Majority of the study participants were from an urban setting and unemployed.
5.3 Presentation and Clinical examination Findings

The presentation and clinical examination findings are shown in table 2.

Table 2: Symptoms and Signs of Outpatients Presenting with Acute Febrile Illness in Outpatient Setting in Eldoret, Kenya.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Symptoms*</th>
<th>Prevalence (N=180)</th>
<th>Signs</th>
<th>Median (IQR)</th>
<th>Vitals</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>72 (40%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>61 (33.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GBM</td>
<td>58 (32.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>35 (19.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>26 (14.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Joint pain</td>
<td>26 (14.4%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>25 (13.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Throat ache</td>
<td>14 (3.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>13 (7.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>10 (5.6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others§</td>
<td>Others§</td>
<td>61 (33.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom duration (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitals</td>
<td>SBP (mmHg)</td>
<td>114(102-128)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DBP(mmHg)</td>
<td>72(64-80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulse rate (beats per min)</td>
<td>104(13.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory rate (breaths per min)</td>
<td>18(3.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symptoms listed as others§ include: coryza, ear ache, epigastric pain, lump, myalgia, nausea, night sweats, nose blockage, poor appetite, rib pain, neck pain, running nose, sweating, Back ache, Body aches, Breast tenderness, Chest congestion, DIB, Dizziness, Dysuria.

Participants recruited into the study had an acute onset of symptoms with median symptom duration of 3 days (IQR 2-4) and majority reported multiple nonspecific
symptoms that included, headache 72 (40%), chills 61 (33.9%) and general body malaise (GBM) 58 (32.2%) as the most common and others including abdominal pain, joint pains, chest pain, throat ache, diarrhea and vomiting.

At presentation the participants had a median temperature of 38.4°C (IQR 38.1-39.0°C). Others vital signs including blood pressure had a lower than normal median systolic blood pressure (SBP) and median diastolic blood pressure (DBP). However, the lower and the upper quartile of SBP contained the normal SBP value. A total of 10(6%) participants had SBP>140 mmHg and a total of 15(9%) participants had DBP>90 mmHg. This resulted in a total of 35 (19%) participants with elevated blood pressure. The average pulse rate among these participants was also high and could have indicated the presence of fever in these patients.

5.4 Prior treatment and use of antimicrobials

Twenty nine (16%) participants had been treated at a different hospital before presenting to the district hospital’s outpatient department. Forty one (23%) participants had previously used antibiotics: 19 (46.3%) of these were self prescribed. Thirty three (18%) had used antimalarials, of which 18 (43.9%) were self prescribed. Participants who had previously used antimalarials were 3 times more likely to have also used antibiotics, OR 2.76 (95% CI, 1.23-6.21). Male participants were more likely to have self prescribed medications compared to the female participants; 25 (69.4%) vs 11 (30.6%) respectively (P=0.02).
5.5 Clinical Diagnoses

The clinical diagnoses made at the district hospital are shown in figure 2. Majority of the participants were diagnosed to have URTI/malaria 35(19.4%), URTI 32(17.8%), malaria 32(17.8%) and pneumonia 32(17.8%) based on the participant presentation, clinical examination and basic laboratory results including RDT for malaria and blood slide for malaria. Eighteen participants had results of other tests which had been performed at the district hospitals before recruitment into the study and included widal and brucellin tests and therefore could have guided the diagnosis in these patients. Diagnoses listed as ‘Other’ diagnoses in figure 2 included; gastroenteritis, lower respiratory tract infections, sepsis, brucellosis, cellulitis, PUD and mastitis.

![Figure 2: Clinical Diagnoses of Patients Presenting with Febrile Illness in Outpatient Setting in Eldoret, Kenya.](image-url)
5.6 Severity of Illness

In this study cohort, 131/180 (72%) participants had feature of sepsis (as defined by the systemic inflammatory response syndrome (SIRS) criteria plus a focus of infection – see Definitions, Page ix-x). Eleven (6.1%) participants had severe sepsis. Ten (91%) out of the 11 patients with severe sepsis had no history of prior antibiotic or antimalarials use.

5.7 Laboratory findings

Laboratory findings of the study participants are as shown in table 3.

**Table 3: Laboratory Results of Patients Presenting with Acute Febrile Illness in Outpatient Setting in Eldoret, Kenya**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>N = 180; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive blood slide + RDT</td>
<td>42 (23.3)</td>
</tr>
<tr>
<td>Positive Blood culture</td>
<td>2 (1)</td>
</tr>
<tr>
<td>HIV test</td>
<td>N=152</td>
</tr>
<tr>
<td></td>
<td>4 (3%, 95% CI: 1%-7%)</td>
</tr>
</tbody>
</table>

Malaria tests were positive for 29 (16%) with RDT and 30 (17%) with blood slide for malaria. Cumulatively, malaria tests (RDT and blood slide) were positive for 42 (23.3%) participants among whom 7 (16.7%) reported history of travel to malaria endemic areas. The median random blood sugar RBS was 5.7 (IQR: 5.2-6.9).

Only 152 out of 180 participants agreed to undergo a HIV test. The remainder declined the test for various social and personal reasons. Of the 4 participants whose HIV test turned positive, 3 were first-time tested and 1 reported to have already initiated care at
Academic Model Providing Access to Healthcare (AMPATH) supported clinic in Uasin Gishu county.

Blood cultures were positive in 2 (1%; 95% CI: 0% - 4%) participants. The 2 gram-negative organisms: sphingomonas paucimobilis and sphingobacterium thalphophilum may have been pathogenic. Among the two patients with positive blood cultures there was no history of prior antibiotic use in the patients with positive blood cultures.

Higher white cell counts (>10X10⁹) were found commonly in patients diagnosed to have pneumonia, URTI/Malaria, typhoid fever and tonsillitis. There was no correlation between elevated white blood cell counts and blood culture positivity.

There were 11 (6.1%) participants with platelet counts less than 100,000 cells/ml. Ten (90.9%) of these patients had positive malaria tests (RDT/blood slide for malaria) and 1 (9.1%) had negative tests for both malaria and bacteremia.

5.8 Management of Participants

A majority of participants 176 (97.7%), were managed as outpatients at the outpatient department (OPD), 3 (1.7%) were referred and 1 (0.6%) was managed as an inpatient at the District Hospital. The participants who were referred and managed as inpatients were participants with signs of sepsis and severe sepsis. Participants requiring intravenous fluids, antibiotics or antimalarials were provided with these interventions before they were allowed home with prescription for medications.
 Among the 87 patients who received antimalarials (shown in figure 3), only 48.3% were confirmed to have malaria by RDT and blood slide for malaria. Participants who were prescribed antimalarial drugs were 85% less likely to receive antibiotics, OR 0.15 (95% CI 0.03-0.71).

Among the 45 participants who received antimalarials without confirmatory malaria diagnostic testing, 15 (26.8%) had a history of prior use of antimalarials before presenting to hospital.

One hundred and sixty seven (92.8%) participants received antibiotics based on the diagnoses listed above. Among the participants who received antibiotics; justifiable
causes for antibiotics (‘justifiable causes’ means all clinical diagnoses that suggested bacterial causes of fever) were 73 (43.7%) as seen in the graph above; 32 (19.2%) pneumonia, 15 (9%) tonsillitis, 12 (7.2%) typhoid fever, and 2 (1.2%) dysentery and others 12 (7.2%) included sepsis, urinary tract infections, brucellosis.
CHAPTER SIX: DISCUSSION

Most studies in Africa on causes of febrile illnesses have been on inpatient and high risk groups including children and HIV infected patients. This study focused on the adult outpatient setting in which there is scarcity of data on causes of fever. Most of the participants presenting with acute febrile illnesses reported non-specific symptoms including headache, chills and general body malaise. Non specific and overlapping symptoms of different febrile illnesses have been reported in several studies in our set up. For example, Crump et al (J. A. Crump, Gove, S., Parry, C. M. , 2011) reported that most adult and adolescent patients presenting to hospital with fever have non-focal signs and symptoms, and another study by Gordon et al demonstrated overlapping features of typhoid and malaria in patients with febrile illnesses (J. A. Crump, Gove, S., Parry, C. M. , 2011; Gordon, 2002; Lutterloh, 2012). Existing data has shown that empiric diagnoses made based on these non specific symptoms (that is using syndrome based approach in making diagnoses) have greatly contributed to misdiagnosis and increased morbidity and mortality (J. A. Crump, 2012; Dougle, 1997; Reyburn, 2004).

Prior use of antimicrobials before presentation to hospital was present in 18.3% and 22.7% for antimalarials and antibiotic use respectively. Among these participants, 51.3% had history of self treatment with antimalarials while 43.9% had history of self treatment with antibiotics. These rates are similar to the meta analysis by Reddy et al in 2010 (Reddy, 2010) that showed antimicrobial use before hospital admission was common with rates ranging from 6-54% in different studies in Africa and a study by Abuya et al in Kenya that showed that 56.8 % adults with acute illness used over the counter medication, 36.9% of which were antimalarials(Abuya, 2007). In contrast, our rates are
much higher than studies by Bigogo et al in western Kenya that showed rates of prior use of antimicrobials before presentation to hospital was 11-24% (Bigogo, 2010), Sumba et al in Nandi Kenya with rates of 19% in adult patients seeking malaria treatment (Sumba, 2008) and the Kenya Integrated Household Budget survey 2005-2006 that had rates of 4% for self diagnosis and treatment in urban areas (Kenya Integrated Household Budget Survey-KIHBS., 2005/06). Diverse reasons have been implicated in self diagnosis and treatment of patients in Kenya including health care cost; distance from health facility; socio-economic and cultural factors (MacKian, 2003). Moreover, in our study, male participants were more likely to have prior history of self treatment and use of antimicrobials compared to female participants, which is in contrast to a study by Breiman et al that did not find a significant difference in health care use/treatment between the sexes but showed that more males were likely to seek healthcare compared to females for episodes of fever (Breiman, 2011). Importantly, several patients in this cohort had either taken a drug they could not identify or had not completed the dose. This practice has been associated with unfavorable outcomes including development of resistance and incomplete treatment of a disease leading to increase in morbidity.

The high numbers of outpatients with sepsis (72%) and severe sepsis (6.1%) show that these conditions are common in patients presenting with febrile illnesses in the outpatient setting. Despite the fact that the largest burden of infectious diseases, and sepsis as a complication, are more prevalent in low and middle income countries, there is scarce data on prevalence and burden of sepsis and severe sepsis in our setting and Africa as a whole (Becker, 2009; Cheng, 2008). Few studies, mostly from Uganda, have demonstrated poor management and increased mortality in patients presenting with sepsis (Cheng, 2008; S.
Notable in our study is the lack of triage area and performance of vital signs at the outpatient departments for patients presenting with acute febrile illnesses. This implies that patients with signs of sepsis and severe sepsis may be missed in these settings, leading to under treatment and increased morbidity and mortality.

Most common diagnoses at the district hospitals were URTI/Malaria, URTI, malaria and pneumonia in this cohort of participants presenting with acute febrile illness. These findings are similar as Kenya estimates that have shown that acute respiratory illnesses and pneumonia are among the most common causes of infection and death in Kenya (Global Antibiotic Resistance Partnership-Kenya Working Group., 2011) but in contrast diarrheal diseases were not as common as has been reported in the same reports. It is possible that the diarrheal diseases were included in the few patients diagnosed with typhoid fever. Malaria was diagnosed more frequently compared to the expected prevalence that has been shown to be decreasing with estimates between 0.1% and 5% in the Rift Valley by Noor et al and the Kenya Malaria Indicator Survey (Division of Malaria Control, 2011; Noor, 2009). This may have been due to overdiagnosis of malaria (in the unconfirmed cases) and malaria positivity in some of the participants who had history of travel to malaria endemic areas.

Laboratory findings in this study showed that white blood cell counts were higher (>10,000cells/ml) in patients with severe febrile illness and pneumonia. Increased white
cell count is a marker of sepsis. Thrombocytopenia was also noted especially in participants who tested positive for malaria. Similar findings have been reported in several studies on malaria and thrombocytopenia (Casals-Pascual, 2006; Ladhani, 2002; Maina, 2010). Thrombocytopenia in malaria has been associated with high parasite burden and severity of disease (Maina, 2010). Many different mechanisms for thrombocytopenia in malaria have been reported including; peripheral destruction, splenic pooling, immune mediated platelet destruction and platelet clumping (Dhanashree, 2004; Maina, 2010).

The HIV rates in this study was 3%, which is similar to the recent preliminary KAIS results that showed decreasing rates of HIV in Kenya with rates in the North rift region decreasing to 3.1%. However our rates could have been higher given that some participants declined to have an HIV test done.

The prevalence of bacteremia in this population was low. The two uncommon gram negative organisms cultured in this study (sphingomonas paucimobilis and sphingobacterium thalphophilum) were likely to be pathogenic, given that our patients presented with fever. Although they are very rare organisms mostly found in water and soil, they have been reported in literature as causes hospital acquired infections. Our prevalence is similar to studies by Feikin et al in western Kenya that showed low prevalence of bacteremia in the outpatient population with acute febrile illness at 1% compared with inpatients reported to be 10% (D. R. Feikin, Geoffrey, J., Barrack, A., Bigogo, G. M., Oundo, J., Beal, B. W., ...Breiman, R. F., 2010a) and in two other recent unpublished studies by Ndegwa (Master’s thesis) and Onchiri (PhD thesis) that showed prevalence of bacteremia to be 3.5% and 3.3% respectively (Ndegwa, Unpublished Msc.
Thesis; Onchiri., Unpublished PhD Thesis). Our results however contrasted with the meta-analysis by Reddy et al, (Reddy, 2010) that showed a mean bacteremia prevalence of 13.5 % in adults with febrile illnesses, although most of the studies included in this meta analysis focused on the inpatient population, and Arthur et al, at KNH that focused on HIV positive adults with prevalence ranging between 21.3%-31.9% over three prospective cross-sectional surveys (Arthur, 2001). The higher prevalence in most regional studies could be attributed to most studies being conducted among inpatients/medical admissions and high risk groups rather than the outpatient population.

Our use of conventional blood culture methods including the recommended period of culture was suitable for most common bacteria (including streptococcus pneumonias, haemophilus influenza, salmonella typhi, Escherichia coli, Klebsiella spp) and therefore could not explain the low prevalence of bacteremia in this study. But, prior antibiotic usage by the participants and low levels of bacteria in blood even in infections with persistent bacteremia like typhoid fever could have influenced the low prevalence of bacteremia in our study population. The collection of one sample for blood culture in this study may have affected our bacterial yield, but most studies on bacteremia in Africa including studies that were included in the meta-analysis of community acquired bacteremia by Reddy et al collected one blood culture sample(Reddy, 2010). There are also limitations of using manual blood culture methods, which we used in this study. Studies have shown increased bacterial yield with automated blood culture compared with manual blood cultures (Çetin E., 2007). We were unable to use automated blood culture systems because it was not available at the period that this study was carried out.
Other causes of febrile illnesses that have recently been reported may have been the cause of the low prevalence of bacteremia in this population. Viruses, mycobacteria, bacterial zoonoses/fastidious bacteria and fungi (especially in the immunocompromised population) have increasingly been reported in several studies as common causes febrile illnesses in our set up. In Kenya, Feikin et al reported that influenza viruses are found more often in outpatients than inpatients in a population in western Kenya(D. R. Feikin, Njenga, M.K., Bigogo, G., Aura, B., Aol, G., Audi, A., ...Breiman, R. F., 2012). Acute HIV infection is also a common cause for presentation with acute febrile illness and has reported to be a commonly missed cause of fever in outpatients presenting with acute febrile illnesses (Prins, 2014; E. J. Sanders, Mugo, P., Prins, H. A., Wahome, E., Thion'go, A. N., Mwashigadi, G., ...Graham, S. M., 2014; E. J. Sanders, Wahome, E., Mwangome, M., Thion'go, A. N., Okuku, H. S., Price, M. A., ...Graham, S. M., 2011). A recent study, although in a different age group of patients, by D’Acremont et al in Tanzania showed that viral causes (81%) were the most common causes of infection in the pediatric population with febrile illnesses (D'Acremont, 2014). This finding was confirmed by a study in Webuye in Kenya by O’Meara et al that showed rickettsiae and viruses to be common in patients presenting with fever(O'Meara, 2015). Bacterial zoonoses including Q fever (Rickettsiae), leptospirosis and brucellosis have also been reported in patients with non malarial causes of fever (Crump, 2013; Knobel, 2013). In this study, we were unable to perform serological tests for fastidious bacteria, cultures for mycobacteria and fungi or viral PCR that could have further characterized and confirmed the etiology of fever in our study population.
Despite an unexpected low prevalence of bacteremia and limitations of defining bacterial causes of fever, our study has several major implications. Firstly, it shows that the prevalence of bacteremia in the adult outpatient setting may be lower than in the inpatient setting and therefore evaluation of the patient will require further tests apart from malaria slide and common bacterial blood cultures. Secondly, the clinical care provider should include other causes of fever (including viruses, mycobacterium and bacterial zoonoses) as differential diagnoses of the underlying cause of febrile illnesses, unless there is clear clinical evidence of a bacterial cause of infection. Thirdly, more regional studies are required to further characterize possible regional causes of fever so as to improve the management of acute febrile illnesses in the outpatient setting.

Overdiagnosis and treatment of clinical malaria is common in the outpatient setting. Eighty seven patients were diagnosed with and treated for malaria despite confirmation of malaria in only 48.3% in this population. However, among the 45 participants treated for malaria without confirmatory tests, 15 (26%) had previously used antimalarials and therefore their treatment could have been based on the presumption of poorly treated/incomplete treatment of malaria and the probability that the antimalarial drugs taken by the participants could have affected the positivity of the malaria tests. Our prevalence of malaria overdiagnosis is similar to the Kenya Malaria Indicator Survey that reported empirical diagnosis of malaria (‘clinical malaria’) at 34% (Division of Malaria Control, 2011). Similarly studies by Dougle et al in Kenya, and Reyburn et al in Tanzania reported prevalences of 59.8% and 54% respectively (Dougle, 1997; Reyburn, 2004). Zurovac et al and Juma et al in Kenya also showed a prevalence of empirical treatment for malaria to be 61.3% and 50.4% respectively (Juma, 2011; Zurovac, 2008). Our results
also show that participants who received antimalarials were also less likely to receive antibiotics. This practice has major implications especially for patients who are treated presumptively for malaria without confirmatory malaria testing. Delays in appropriate antibiotic therapy for bacterial infections has been shown to increase morbidity and mortality (Dougle, 1997; Reyburn, 2004)

Our results have also shown antibiotic overuse among patients with febrile illnesses. Ninety three percent of study patients; of whom 80 (44%) had diagnoses of URTI, malaria or URTI/Malaria. However, the use of antibiotics was justifiable (based on clinical diagnosis indicating likely cause as bacterial infection) for 73 (43.7%) participants who presented with clinically evident signs a bacterial infection. This practice has been widely reported by several studies in our set up and has been associated with the development of antimicrobial resistance (Global Antibiotic Resistance Partnership-Kenya Working Group., 2011; Okeke, 2003).
CHAPTER SEVEN: CONCLUSIONS AND RECOMMENDATIONS

7.1 Conclusion

Patients with acute febrile illness can present with non specific but severe symptoms; sepsis and severe sepsis in the outpatient setting. Laboratory work up other than blood slide for malaria and blood culture is important in ascertaining diagnosis and assessing severity of illness in these patients. A number of patients with acute febrile illness receive antimicrobials without definite diagnosis.

7.2 Recommendations

Triage of patients presenting with acute febrile illnesses will assist in identifying those with severe symptoms. Ministry of Health guidelines on confirmatory diagnosis and treatment of malaria should be upheld. We recommend larger local studies to look for other causes of acute febrile illnesses other than blood cultures and blood slide for malaria and to define the role played by other causes of acute febrile illnesses; bacterial zoonoses/fastidious bacteria, viruses and mycobacterium. These studies would inform development of clear and region-specific guideline development for comprehensive management of febrile illnesses that would assist clinicians in the outpatient settings in management of patients with acute febrile illnesses especially in areas without capabilities to complex microbiologic tests.
REFERENCES


adults seeking care for fever: a systematic review and audit of current practice. 

*International Health, 6*(2), 82-92.


APPENDICES

APPENDIX I: Data collection form

Participant’s Number __ __ __ __  Today’s Date: __ / __ / __

General

1. Patient being seen in: ☐ Outpatient Department

2. Documented fever (tympanic temperature > 38°C): ☐ Yes ☐ No

Demographics

4. Year of Birth: __ __ __ __ (Include only 1995 or earlier)

5. Date of Birth if known: __ / __

   day / month

6. Sex: ☐ Male ☐ Female

7. Occupation: ________________________________________________ (ex. Unemployed, farming etc)

8. Residence: ☐ Rural ☐ Urban

9. Presenting Complaints:

   __________________________________________________________________________________

   __________________________________________________________________________________

10. Duration of symptoms:

    __________________________________________________________________________________

11. Previous antibiotic use: ☐ Yes ☐ No

    List:

12. Previous antimalarial use: ☐ Yes ☐ No Name:
List:

__________________________________________________________________

12. Previous treatment at a different hospital:  ☐ Yes  ☐ No

Diagnosis (if known):

__________________________________________________________________

Physical Examination:

13. Vitals:

Blood Pressure: _____________mmHg

Heart Rate: __________/minute

Respiratory rate ____________breaths/minute

Temperature: _____________\(^0\)C

Physical Exam findings:

__________________________________________________________________

__________________________________________________________________

Patient Management

Patient managed:  ☐ Outpatient  ☐ Inpatient/Referred

If inpatient, outcome?  ☐ Discharged  ☐ Died

16. Diagnosis at OPD: _______________________________________________

17. Treatment provided: Antibiotics:  ☐ Yes  ☐ No

Antimalarials:  ☐ Yes  ☐ No

If Yes, list ________________________________________________________

__________________________________________________________________
Test Results

18. HIV Test: ☑ Positive ☐ Negative

19. Random Blood Sugar Results: ________________

20. CD4 Count: __________________________

   RDT for malaria: ☑ Positive ☐ Negative

22. Full Haemogram: WBC: _________   HB: ________   Plt: __________

23. Blood Culture result:
   Anaerobic:
   ___________________________________________ ____________________
   Aerobic:
   ___________________________________________

24. Antibiotic Susceptibility Testing: (Attach Results)
INFORMED CONSENT STATEMENT

Bloodstream Infections in Patients Presenting with Fever at Uasin Gishu District Hospital, Eldoret, Kenya

INTRODUCTION:

You are being asked to participate in this research study because you have fever which is a body temperature above 38°C. This study is being conducted by Dr. S. M. Ali who is a postgraduate student at the Department of Medicine, Moi University. This consent form gives you information about the study. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep. The doctor in charge of this study at this site is Dr. S. M. Ali. Before you decide if you want to be a part of this study, we want you to know all about it.

STUDY PURPOSE:

The purpose of this study is to find out number of people who have infection in their blood when they present to hospital with fever.

Please note that:
• It is entirely your choice whether or not you participate in this study.

• You may stop taking part in the study at any time.

• You will still receive your standard health care if you do not participate in this study.

**NUMBER OF PEOPLE TAKING PART IN THE STUDY:**

If you agree to participate, you will be one of a minimum of 180 people who will take part in this study. You will be in this study for just one day (today).

**PROCEDURE FOR THE STUDY:**

If you agree to be in the study, you will only need to participate today. You will not need to come back in the future as part of this study. The evaluations will take about ½ to 1 hour to complete.

**Screening Encounter**

After you have read and signed this consent form, you will have several evaluations done to make sure that you meet the requirements for joining the study.

- You temperature will be taken again to confirm that you have high temperature.

**Entry into the Study**

If all of your screening evaluations show that you can join this study, you will have more information collected today during this clinic visit.
You will not be asked to take any medications, make any changes to your lifestyle or come back to clinic any more regularly than you already do. You will not need to do anything out of the ordinary after all of the evaluations have been collected.

**Evaluations**

Also at this visit, you will have the following evaluations:

- You will have a clinical (physical) examination
- You will be asked questions about your health and about the medicines you have been taking.
- About 20mL (5 teaspoons) of blood will be drawn for lab tests, two blood cultures which checks for any infection in the blood, HIV, complete blood count, malaria slide and rapid test to check if you have malaria and blood sugar level to check if you have diabetes.

Throughout the study, results of tests will be made available to your doctor as soon as they are received. Knowing the results may assist your medical care.

While participating in this research, your identity will remain confidential and will not be available under any circumstances to other researchers except those involved in this research.

All information collected during this research study will not be released to anyone in a way that could identify you, including you or other family members.

**RISKS OF TAKING PART IN THE STUDY:**
Risks of Blood Drawing

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, light-headedness, and in rare cases, fainting or infection.

Risks of Breach of Confidentiality

Although the investigators will take care to maintain confidential records, taking part in this study may risk your medical information becoming known to other people.

BENEFITS OF TAKING PART IN THE STUDY:

If you participate in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. You will be investigated more thoroughly than if you were not part of this study, which may help you to feel better. Information learned from this study may help others who have fever in Kenya and other parts of East Africa. Information learned from this study may also help improve the ability of people to get evaluated if they have fever.

ALTERNATIVES TO TAKING PART IN THE STUDY:

Instead of being in this study you have the choice of not taking part and having your usual care today. If you refuse to take part in the study, you will still receive the usual treatment you would get.

CONFIDENTIALITY:

The results of your physical exam and blood tests will be shared with your doctor. However, it will not be possible to identify you individually from this information. The
study team will provide you with an identification number. The identification number (not your name or other information that could be used to identify you) will be used for laboratory tests. Any publication of this study will not use your name or identify you personally. Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be revealed if required by law. Your records may also be reviewed by the Moi Teaching and Referral Hospital/Moi University Institutional Research and Ethics Committee, the Kenya Ministry of Health and study staff.

COSTS:

You will not pay for study-related visits, physical examinations or laboratory tests.

PAYMENTS/COMPENSATION:

There is no monetary compensation for the time invested in completing study related evaluations.

CONTACTS FOR QUESTIONS OR PROBLEMS:

For questions about the study or a research-related injury, contact the researcher Dr. S. M. Ali at 0724231874. For questions about your rights as a research participant or complaints about a research study, contact the Institutional Research and Ethics Committee (IREC) office at 053-2033471/2/3/4 ext 3008.

VOLUNTARY NATURE OF STUDY:
Taking part in this study is completely up to you. You may choose not to take part in this study. You may leave this study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let us know.

PARTICIPANT’S CONSENT:

In consideration of all of the above, I give my consent to participate in this research study. I have read this consent form (or had it read and explained to me), all my questions have been answered, and I agree to take part in this study. I acknowledge receipt of a copy of this informed consent statement.

PARTICIPANT’S SIGNATURE OR MARK: ____________________________ Date: __________

SIGNATURE OF WITNESS: __________________________________________ Date: __________

SIGNATURE OF PERSON OBTAINING CONSENT: __________________________ Date: __________
APPENDIX III: Swahili Informed Consent

HOSPITALI YA RUFAA NA MAFUNZO YA MOI/KAMATI YA TAFITI NA MAADILI YA CHUO KIKUU CHA MOI

Pendekezo La Kuchunguza Maradhi Ya Bakteria Kwa Damu Kwa Wagonjwa Wanaohudhuria Hospitali Wakiwa na kiwango cha Joto la Juu katika Hospitali ya Uasin Gishu District, Eldoret, Kenya

UTANGULIZI:


LENGO LA UTAFITI

Lengo la utafiti huu ni kuchunguza kiwango cha watu walio na maradhi ya bacteria kwa damu kati ya wale wanaokuja hospitalini na kiwango cha juu cha joto.

Tafadhali jua kuwa:
• Ni chaguo lako binafsi kushiriki au kutoshiriki katika utafiti huu.
• Unaweza kujiondoa kwenye utafiti wakati wowote.
• Bado utaendelea kupokea huduma yako ya kiafya ya kawaida hata kama hutashiriki katika utafiti huu.

**IDADI YA WASHIRIKI KATIKA UTAFITI**

Ikiwa utakubali kushiriki, basi utakuwa mmoja wa watu wasiopunguka 180. Utashiriki katika utafiti huu kwa siku moja pekee (yaani leo).

**UTARATIBU WA UTAFITI:**

Ikiwa utakubali kuwa katika utafiti huu, basi utahitaji kushiriki leo tu. Hutahitaji kuja baadaye kama sehemu ya utafiti huu. Uchunguzi utachukua muda wa kati ya nusu saa na saa moja.

**Ziara ya Uchunguzi**

Baada ya kusoma na kujaza fomu hii ya idhini, utafanyiwa majaribio kadhaa ili kuhakikisha kuwa utafiti huu kwa kuku rhusu kushiriki katika utafiti huu.

• Utapimwa tena joto mwilini kuhakikisha kwamba una joto zaidi ya 38°C

**Ziara ya Kuingia kwenye Utafiti.**

Ikiwa majaribio yote yataonyesha kuwa unaweza kushiriki katika utafiti huu, basi utafanyiwa uchunguzi zaidi katika ziara hii ya leo.
Hautahitajika kutumia dawa zozote, kubadilisha kwa vyovyote jinsi unavyoishi au kurudi kwenye kliniki kwa ziara zaidi ya zile za kawaida. Hautahitajika kufanya jambo lolote lisilo la kawaida baada ya majaribio yote kufanywa.

**Majaribio**

Katika ziara hii pia, utafanyiwa majaribio yafuatayo:

- Utapimwa kiwango cha joto mwilini
- Utafanyiwa uchunguzi wa mwili na kuulizwa maswali juu ya afya yako na kuhusu madawa unazomeza.
- Karibu mililita 20 (vijiko vitano vidogo) ya damu itatolewa kwa ajili ya majaribio, blood culture inayopima kama una infection ya bacteria kwa damu, HIV, utapimwa CBC inayopima kiwango ya damu, utapimwa malaria na kiwango cha sukari katika damu ili kuangalia kama una ugonjwa wa kisukari.

Wakati wowote wa utafiti, matokeo ya majaribio yatapewa daktari wako pindi tu yatakapopokelewa katika kliniki. Kujua matokeo haya kunaweza kusaidia katika kukuhudumia kimatibabu.

Ukishiriki katika utafiti huu, kitambulisho chako kitabaki siri na haitapatikana kwa watafiti wengine kamwe. Habari zote zitakazokuswa katika utafiti huu hazitatolewa kwa mtu yeyote kwa njia ambayo inayoweza kukutambulisha, wewe au watu wa familia yako.
HATARI ZA KUSHIRIKI KATIKA UTAFITI HUU

Hatari za Kutolewa Damu

Kutolewa damu kunaweza kusababisha kukosa raha, kutokwa na damu, au kuvilia katika sehemu inayodungiwa, kizunguzungu na kwa nadra sana, kupoteza fahamu au kupata uambukizo.

Hatari za Kuvunja Usiri

Ingawa mtafiti atajitahidi kulinda rekodi zako, kushiriki katika utafiti huu kutazua hatari ya kujulikana kwa habari zako za afya na watu wengine.

FAIDA ZA KUSHIRIKI KATIKA UTAFITI HUU


CHAGUO ZINGINE ULIZO NAZO IKIWA UTAAMUA KUTOSHIRIKI KATIKA UTAFITI HUU.
Badala ya kujiunga na utafiti huu, unaweza ukaamua kutoshiriki na uendelea kupokea huduma zako za kawaida. Uamuzi wako wa kutoshiriki hautaathiri huduma ambazo utapokea.

**USIRI**

Matokoeo yako ya uchunguzi wa mwili na uchunguzi wa damu yatapewa daktari wako. Hata hivyo, haitawezekana kwa mtu yeyote kukutambua wewe binafsi kwenya taarifa hizi. Timu ya watafiti itakupatia nambari yako ya utambulisho. Nambari hii (ambayo si jina au habari zingine zinazoweza kutumiwa kukutambua) itatumiwa kwa testi ya damu.


**GHARAMA**

Hutalipia ziara zozote zinazohusiana na utafiti, uchunguzi wa mwili, majaribio ya kimaabara au uchunguzi wowote utakaofanywa.

**MALIPO/FIDIA**

Hautapata malipo ya fidia yoyote kwa wakati utakaotumia kuhudhuria majaribio ya utafiti.

**WATU UNAOWEZA KUWASILIANA NAO UKIWA NA MASWALI AU MATATIZO YOYOTE.**

Ikiwa una maswali yoyote au jeraha lolote zinazohusiana na utafiti huu, wasiliana na Dkt. S. M. Ali kwa nambari 0724231874. Kwa maswali kukuhusu haki zako kama mshiriki
katika utafiti au malalamiko kuhusu utafiti, unaweza kuwasiliana na Kamati ya Tafiti na Maadili ya Chuo Kikuu Cha Moi (IREC) kwa nambari 053-2033471/2/3/4 ext 3008.

**KUSHIRIKI KATIKA UTAFITI KWA KUJITOLEA KWA HIARI**


Tutakupasha habari zozote mpya, kuhusu utafiti huu au tafiti zingine, zinazoweza kuathiri afya yako, ustawi wako au uamuzi wako wa kushiriki katika utafiti huu. Tafadhali tujulishe ikiwa utataka matokeo ya utafiti huu.

**IDHINI YA MSHIRIKI**

Kwa kuzingatia haya yote, natoa idhini yangu ya kushiriki katika utafiti huu. Nimiesoma fomu hii (au nimesomewa na kufanuliwa yaliyomo), maswali yangu yote yamejibiwa, na ninakubali kushiriki katika utafiti huu. Ninakubali kuwa nimepokea nakala yangu ya fomu hii ya idhini.

**SAHIHI AU ALAMA YA MSHIRIKI:**

MSHIRIKI: ___________________________________________ Tarehe: _______

**SAHIHI YA SHAHIDI:**

SHAHIDI: ___________________________________________ Tarehe: _______

**SAHIHI YA ANAYETAKA**

IDHINI: ___________________________________________ Tarehe: _______

**APPENDIX IV: IREC Approval**