ADVERSE SKIN REACTIONS TO SULFADOXINE-PYRIMETHAMINE IN WESTERN KENYA: IMPLICATIONS FOR MALARIA TREATMENT STRATEGIES.

BY

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DECLARATION

This Thesis is my original work and has not been presented for a degree in any other University.

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To my beloved parents.
ABSTRACT

With the increasing problem of chloroquine-resistant *falciparum* malaria in Kenya, treatment with alternative drugs such as sulfadoxine-pyrimethamine is becoming common. One of the side-effects associated with the use of this drug is adverse skin reactions. Hospital-based retrospective and prospective studies of adverse skin reactions to sulfadoxine-pyrimethamine were undertaken in a holoendemic malaria area of western Kenya in order to understand the implications of treatment policies. In a retrospective study of 35,950 medical records for all conditions recorded between 1994-1995 in Kisumu District Hospital, only a small proportion (9.0%) were patients diagnosed with skin events. No cases of drug-induced skin reactions were diagnosed during this time period. In a retrospective study of 1,557 documented skin events from 1994-1995 in the outpatient skin clinic in New Nyanza Provincial General Hospital, drug-induced reactions constituted only 1% (16 cases). From a 12-month prospective study, a total of 33 patients were enrolled into the study. Ten of the 33 patients had sulfadoxine-pyrimethamine minor skin reactions. There were no fatalities associated with sulfadoxine-pyrimethamine. Since the skin reactions are minor and not a major public problem, it is recommended that sulfadoxine-pyrimethamine may be used for the treatment of chloroquine-resistant *falciparum* malaria.
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DEFINITIONS

Adverse drug reaction - A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. An adverse event which is judged to be caused by the drug (Phillips-Howard and Bjorkman, 1990).

Case reports - Reports of the experience of patients, all of who have a common exposure, examining what their clinical outcomes were (WHO, 1990).

Chemoprophylaxis - Protection from or prevention of disease by use of drugs (WHO, 1990).

Drug resistant malaria parasite - Has been defined by the World Health Organization as the “ability of a parasite to multiply or survive in the concentrations of a drug that normally destroy parasites of the same species or prevent their multiplication. Such resistance may be relative (yielding to increased doses of the drug tolerated by the host) or complete (withstanding a maximum dose tolerated by the host)” (WHO, 1963).

Epidemic - A temporary period of large scale prevalence of a given disease in a population.

Epidemiology - Study of the distribution and determinants of diseases in populations.

Fixed drug eruptions - Drug induced skin reactions characterized by lesions that recur on the same site when exposed to the same drug. They may arise within an hour or two of taking the drug as discs of erythema, either singly or multiple and severe reactions may produce a solitary bullae at the centre of the disc. The lesion subsides quickly when the drug is stopped leaving a disc of pigmentation which may persist until next attack.

High-risk group - A group in the community with an elevated risk of disease.

Holoendemic (stable) area - An area with high malaria transmission with very little variation with season (Moll, 1992).

Morbidity - Any departure, subjective or objective, from a state of physiological or psychological well-being (Moll, 1992).

Mortality - Number of deaths in a specified period of time (Moll, 1992).

Parasitaemia - Condition in which infecting parasites are present in the blood.

Prevalence - The number or proportion of cases or events or conditions in a given population.

Prophylaxis - Any method of protection from or prevention of disease; when applied to chemotherapy it is commonly designated as “drug prophylaxis” or “chemoprophylaxis”
Prospective study - Investigations performed simultaneously with the events under study.

Retrospective study - Investigations conducted after events under study.

RI level - Parasitaemia level of *Plasmodium falciparum* decreases one to three weeks after termination of treatment. This level is based on WHO grading system of *in vivo* resistance to normal doses of chloroquine (WHO, 1990).

RII level - Parasitaemia level of *Plasmodium falciparum* decreases with treatment but does not disappear during the first week of treatment. This is level based on WHO grading system of *in vivo* resistance to normal doses of chloroquine (WHO, 1990).

RIII level - No decrease or increase in the parasitaemia level of *Plasmodium falciparum* during the first week of treatment. This level is based on WHO grading system of *in vivo* resistance to normal doses of chloroquine (WHO, 1990).

Risk - The probability that an event will occur e.g. that an individual will become ill or die within a stated period of time or age (WHO, 1990).

Risk factor - An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of a disease or other health-related event or condition.

Severe drug reaction - Defined as fatal, life-threatening, disabling or incapacitating reaction to a drug (Phillips-Howard and Bjorkman, 1990).

Stevens-Johnson syndrome - Drug induced skin reaction characterized by an illness in which, the cutaneous lesions of erythema multiform are accompanied by bullae, ulceration of the conjunctivae, mouth, and genitalia, with fever.

Side effect - Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the drug.

Surveillance - Ongoing scrutiny, generally using methods distinguished by their practicability, uniformity and rapidity, rather than by complete accuracy. Its main purpose is to detect changes in trends or distributions in order to initiate investigative or control measures.
CHAPTER ONE
INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Malaria is an acute and chronic disease caused by an obligate intracellular protozoan of the genus *Plasmodium*. Four species infect man and they are: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. All the four species of *Plasmodium* exist in Kenya. *P. falciparum*, is the most prevalent species in all endemic areas, accounting for more than 80-90% of infections in Kenya. *P. malariae*, the second most prevalent species, accounts for about 10%, *P. ovale* 5%, while *P. vivax* is very rare (Roberts, 1974). These parasites are transmitted from man to man by anopheline mosquitoes in which part of the life cycle takes place (Figure 1).

The vector species of *Plasmodium* in Kenya are members of the *Anopheles gambiae* complex and *An. funestus*. The important members of *An. gambiae* complex are *An. arabiensis* and *An. gambiae sensu stricto*. The latter has been identified from the Nandi foothills from where it is spread up to the shores of Lake Victoria, the North-west of Kisumu (Service, 1978). *An. arabiensis* is more common in the plains to the South of Kisumu Town and less frequent in the North-west of Kisumu (White, 1972; Flighton et al., 1979).

It has been estimated that the incidence of malaria in the world may be in the order of 300-500 million clinical cases each year, with tropical Africa accounting for more than 90%. Estimates of malaria mortality vary from 1.5 to 2.7 million deaths world-wide per year, with the greatest majority in Africa. Approximately 1 million deaths among children under 5 years of age in Africa is attributed to malaria (WHO, 1996).
The then highest infant mortality rates in Kenya, ranging between 139 and 155 per 1000 were reported in Saradidi, which is about 50 km from Kisumu (Spencer et al., 1987a). Later studies conducted in Kisumu revealed that malaria was responsible for between 20 to 30% of the infant mortality in that area (WHO, 1994a).

According to the Kenya Ministry of Health (MoH, 1992), patterns of malaria transmission in Kenya are described in terms of stable and unstable. Stable occurs in most parts of the Coast, Nyanza, and Western Provinces. Transmission of malaria is high with the number of infective bites per person ranging from as little as 5 to 52 per year (MoH, 1992). The burden of morbidity and mortality falls on infants and young children. Older age groups in this situation can maintain high levels of clinical immunity, except under special circumstances, such as pregnancy, where clinical manifestations may reappear. Unstable malaria occurs in areas of lower endemicity such as the Eastern and Rift Valley Provinces. The endemicity patterns of malaria in Kenya are illustrated in the map (see Figure 2).

Documented reports of malaria control in Kenya date back to the work of Garnham in 1929, when malaria control consisted of anti-larval activities such as oiling water pools and surface drainage. Due to the abundance of breeding sites, this approach was not feasible, thus necessitating the adoption of public health and chemotherapy as the other viable options (Garnham, 1929).

In the absence of vector control measures, malaria containment depends on prompt and effective chemotherapy. Due to its low cost, safety, wide availability and high efficacy in the treatment of three species of malaria parasites in sub-Saharan Africa, chloroquine has been the preferred therapy for malaria. In Kenya, clinical resistance to chloroquine is now at a level where it cannot be considered as the drug of first choice for malaria therapy (WHO, 1990). According to the Kenya Ministry of Health (MoH, 1992), the drug of first choice is to be a combination of sulfadoxine and pyrimethamine. This drug combination has been documented to cause adverse skin reactions. This study will provide
the baseline information on the skin reactions associated with sulfadoxine-pyrimethamine before the policy on this drug combination is implemented as a first line therapy for malaria.
Figure 1: The life cycle of *malaria* parasite.

(Adapted from Webster, 1990)
Figure 2: Endemicity of malaria in Kenya.
1.2 LITERATURE REVIEW

1.2.1 Malaria control strategies in Kenya.

High morbidity and mortality together with poor socio-economic conditions prevailing in Africa dictate the urgent need to study effective and affordable malaria control strategies. In Kenya, malaria control efforts have traditionally relied on environmental management, larviciding, residual indoor spraying, contact reduction and on chemotherapy.

(i) Environmental management

Clearing of bushes and tall grass around households and water reservoirs (that is ponds, dams, tanks, sewage disposal sites) and regular clearing of vegetation surrounding irrigation canals, help in the elimination of larval development sites.

(ii) Larviciding

Chemical larvicides include petroleum oils and pesticides such as temephos and fenthion. Many promising leads for the biological control of anopheline mosquitoes have been identified e.g. the spore-forming bacterium, *Bacillus thuringiensis israelensis* which acts as a larvicide against a broad spectrum of mosquito species; various species of larvivorous fish such as *Gambusia* species or *Lebistes* species. Seeding of fish (*Tilapia zilli*) in water bodies has been used in many ponds, dams and lakes as a larval feeder for control measures (Roberts, 1974).

The validation of these approaches and the determination of their operational potential require extensive field trials in Kenya.
(iii) Residual indoor spraying

In the period 1955-1957, about 6000 houses in Nandi district were annually sprayed with dieldrin. Malaria transmission was interrupted until when localized epidemics began to reoccur (Roberts, 1964).

In 1976, large scale indoor spraying of fenitrothion as a residual insecticide was carried out on the banks of Lake Victoria. The general mortality decreased from 23.9 to 13.5 deaths per 1000 population and infant mortality from 157 to 93 per 1000 live births (Payne et al., 1976).

With the outbreak of epidemic malaria in Uasin Gishu District in 1988, indoor spraying was done in houses in areas with high mosquito densities using 10% cyfluthrin, a synthetic pyrethroid. Malaria transmission was interrupted (Ngindu et al., 1989). Since then, no other large scale projects involving spraying with residual insecticides have been carried out in Kenya.

(iv) Contact reduction

Bed nets impregnated with insecticides, for malaria prevention in different settings in Africa have been evaluated. In The Gambia, bed nets impregnated with permethrin have been shown to have an impact on malaria related child mortality (D’Alessandro et al., 1995a). In Kenya, impregnated bed nets have been shown to reduce the incidence of P. falciparum infections (Sexton et al., 1990; Beach et al., 1993; Nevill et al., 1996). There is a need however, for studies to assess the impact of insecticide-impregnated bed nets on malaria morbidity and mortality under standard conditions in varying endemic situations in Kenya. Malaria has been controlled in many areas of the world by the use of insecticides to kill the *Plasmodium*-carrying mosquito or by destruction of the mosquito habitat.

(v) Vaccines

The foregoing methods have not been practical or cost-effective across much of Africa or in regions of Latin America, making a vaccine the best alternative. Much research has focused on developing effective malaria vaccines. Experimental vaccines are being developed against various stages in the parasite’s life cycle: the sporozoite, the liver schizonts, the asexual erythrocytic parasites
and gametocytes. Vaccines derived from a sexual-blood-stage antigens are of special interest in Africa, because they mimic the development of natural immunity in children living in endemic areas.

Furthermore, such vaccines induce long-term immunity because of natural boosting. The "SPf66" was the first such vaccine to be tested in man (Alonso et al., 1994). Trials conducted in Africa with the SPf66 vaccine have shown variable results, with the Tanzanian trial having an estimated efficacy of 31% (Alonso et al., 1994) and The Gambian trial 8% (D’Alessandro et al., 1995b).

(vi) Drugs

In several parts of the world, malaria control is based on the administration of drugs to reduce mortality and to shorten illness. This is particularly the case in Kenya, where malaria incidence is particularly important.

In Kenya, mass chemotherapy and prophylaxis with antimalarial drugs were carried out in the early 1950s and in the mid 1960s. In the period 1953-1955, pyrimethamine mass chemotherapy was carried out in Nandi District. 120,000 persons were treated annually and a reduction in parasite rates from 23% to less than 3% was noted (Roberts, 1956).

Published reports (Roberts, 1974) exist on chloroquine and pyrimethamine mass chemotherapy, on a two weekly basis, in Malindi and Kwale Districts in 1958, and in Kisumu Township in 1966. A reduction in parasite rates from 18% to less than 5%, 15 to less than 6% and 23 to less than 3% were noted for Malindi, Kwale and Kisumu respectively.

The study implemented between 1981-1984 in Saradidi, is regarded as the only one so far undertaken on the subject of community participation involving the use of antimalarial drugs in Kenya. Malaria was recognized as the most important health problem and as a consequence it was decided to provide treatment with chloroquine to all persons presenting with fever or other symptoms of malaria, and to give chemoprophylaxis to pregnant women. At the end of the project, little impact was
observed on malaria prevalence, largely attributable to emerging chloroquine resistance in this holoendemic area (Spencer et al., 1987b).

In 1988, an outbreak of epidemic malaria occurred in Uasin Gishu District. Control measures were instituted immediately in form of antimalarial drugs. Chemotherapy with oral and parenteral chloroquine was provided to health institutions for treatment of both inpatient and outpatient cases, and short term chemoprophylaxis using chloroquine was carried out in school pupils and communities near health institutions (Ngindu et al., 1989). Since then, no other large scale projects involving the use of antimalarial drugs for chemotherapy have been carried out in Kenya.

1.2.2 Resistance to antimalarial drugs in Kenya

Kenya is one of the countries listed by the World Health Organization (WHO) as having chloroquine-resistant strains of *P. falciparum* (WHO, 1982).

The first report of chloroquine-resistance, satisfying the WHO test criteria, concerned a USA citizen who had contracted the disease in Kenya in 1978 (Kean, 1979). Similarly, resistance at the RI level, was reported in non-immunes in Kenya (Fogh et al., 1979). Since then chloroquine-resistance of *P. falciparum* in semi-immunes has been reported from Kenya (Spencer et al., 1983; Sixsmith et al., 1983). In 1984, cases of RII and RIII resistance started emerging from the Coast area. Away from the coast, in Saradidi, near Kisumu in western Kenya, where chloroquine was used extensively in a malaria project, resistance was reported (Spencer et al., 1987b). However, the prevalence of chloroquine-resistant strains reported from western Kenya is much less than from the coast (Masaba and Spencer, 1982; Spencer et al., 1982 Watkins, et al, 1987a). Chloroquine resistant *P. falciparum* has spread to areas characterized by unstable malaria, such as Kakamega. For instance it was reported that 36% of the cases from a study group of 56 individuals had an RIII response in this area (Keuter et al., 1990). In Kisumu, resistance to 4-aminoquinolines is widespread, and about 50% of the strains are resistant to
chloroquine at the RII level (Oloo et al., 1991). The RI and RII type chloroquine resistant \textit{P. falciparum} have been reported in Kisumu (Oloo et al., 1986). Pyrimethamine has lost its use in Western Kenya as resistance is widespread with Kisumu isolates showing 100\% non-sensitivity (Nguyen-Dinh et al., 1982). In view of the failure of chloroquine in providing adequate chemoprophylaxis, chlorproguanil was evaluated as a weekly single dose alternative, but adequate protection was not achieved around Malindi (Watkins et al., 1987b). Standard doses of quinine are still effective against \textit{P. falciparum} and no serious problems have been reported with sulfadoxine-pyrimethamine or pyrimethamine-sulfalene (Watkins et al., 1987c). Amodiaquine and chloroquine at the RI and RII levels of resistance have been reported from Nyanza Province (Kariuki et al., 1988). An excellent account of resistance of \textit{P. falciparum} to 4-aminoquinolines and antifolates in Africa is given by Schapira (1990). In the highlands of Kenya, resistance to amodiaquine and chloroquine is widespread, and 27\% and 73\% of the strains are resistant to amodiaquine and chloroquine respectively (Khan et al., 1991). From the coast, chloroquine resistance at a rate of 60\% has been reported (Hagos et al., 1993). The RII type of chloroquine resistant \textit{P. falciparum} have been reported in 60\% of the children treated with chloroquine in Siaya District hospital, Western Kenya (Bloland et al., 1993).

1.2.3 Malaria drug policy in Kenya

The problem of resistance to antimalarial drugs especially chloroquine, has become a major concern for managers of malaria control programmes throughout the world. The malaria treatment policy should define the first-line drug to be used, taking account of the best available information on resistance (WHO, 1990). It is generally recommended that the alternative to chloroquine in Africa, is to be sulfadoxine-pyrimethamine, to which there is at present little resistance (WHO, 1990). With the emergence of chloroquine resistance throughout East Africa, antifolate sulfonamide combinations are
used increasingly for the treatment of non-severe malaria. In Kenya, sulfadoxine-pyrimethamine is to be recommended as first-line drug in the treatment of malaria (MoH, 1992).

The detailed guidelines for standard treatment of *P. falciparum* is to be based on the following principles (MoH, 1992):

1. The drug of first choice for all children aged 5 years or less and for all non-immune patients is to be a combination of pyrimethamine with sulfadoxine. In the case of patients aged 6 years or more who have lived continuously in stable endemic areas and who have non-severe malaria, chloroquine at standard dosage is to be the drug of choice. The progress of such patients is to be reviewed after 24 hours and thereafter as necessary. In case of poor response to initial treatment, therapy is to be changed to sulfadoxine-pyrimethamine combination.

2. Intramuscular sulfadoxine-pyrimethamine is to be used in the treatment of patients who cannot take oral therapy, but who otherwise do not have features of fever or complicated malaria and in the initiation of therapy for patients with severe malaria, prior to their transfer to a health facility able to provide parenteral quinine.

3. Pregnant women with malaria are to be treated promptly with sulfadoxine-pyrimethamine.

1.2.4 Previous studies on the efficacy of sulfadoxine-pyrimethamine in Kenya

In areas of intense chloroquine resistance, where chloroquine fails to effect sustained clinical improvement or haematological recovery, sulfadoxine-pyrimethamine is to be recommended as a first-line therapy (WHO, 1994b).

Sulfadoxine-pyrimethamine is an attractive treatment in view of its simple dose regimen, long action, low cost, and ready availability (Gozal and Hengy, 1990; Nevill and Watkins, 1990).

Sulfadoxine-pyrimethamine, because of its long residence time in the body, serves two clinical purposes in malaria treatment. It rapidly eliminates the parasite population responsible for illness, and
then ensures an infection-free period for the host, during which physiological recovery is facilitated (Watkins and Mosobo, 1993).

Documented reports on the efficacy of sulfadoxine-pyrimethamine date back to the work of Roberts in 1967-1968, when a preliminary field trial of the long acting sulfonamide, sulfadoxine, alone, and in combination with pyrimethamine, as a malaria suppressant was conducted in western Kenya. The results were best in the group that received sulfadoxine-pyrimethamine combination than in the other two groups who received either chloroquine or sulfadoxine alone (Roberts, 1970).

Field studies conducted in Kisumu, Kenya to assess the susceptibility of local strains of *P. falciparum* to pyrimethamine alone (by standard 7-day *in vivo* and *in-vitro* tests) demonstrated that pyrimethamine resistance was very common. Parasite susceptibility to sulfadoxine-pyrimethamine was uniformly greater when the isolates were tested *in-vivo* thus indicating that this drug combination remains potent despite high frequency of resistance to pyrimethamine alone (Nguyen-Dinh et al., 1982).

The World Health Organization advocates sulfadoxine-pyrimethamine for the treatment of chloroquine-resistant *falciparum* malaria in pregnancy (WHO, 1984). From a study on the comparison of treatment and protection against falciparum malaria in pregnant and non-pregnant women with chloroquine, sulfadoxine-pyrimethamine, chlorproguanil and dapsone, in Kakamega District, Kenya, it was observed that clearance of parasites was better with sulfadoxine-pyrimethamine than with chlorproguanil, dapsone and chloroquine. Longest protection was obtained with sulfadoxine-pyrimethamine (Keuter et al., 1990).

As chloroquine-resistant *P. falciparum* becomes prevalent, more febrile children treated with chloroquine are likely to remain parasitaemic, febrile and at risk of anaemia, severe illness and death. Sulfadoxine-pyrimethamine as an alternative drug for the first-line treatment of malaria related fever in
children in western Kenya, was observed to be more effective in maintaining clinical improvement and complete parasite clearance than treatment with chloroquine. Consequently, chloroquine can no longer be considered effective therapy of clinical *P. falciparum* in children less than 5 years in western Kenya (Bloland et al., 1993).

Sulfadoxine-pyrimethamine was introduced into the Kenyan market in 1983 and its use was limited to the treatment of chloroquine-resistant cases. This was followed by the introduction of sulfalene-pyrimethamine and amodiaquine. A few years after this, a study was conducted to compare the efficacy of these three drugs. Rural school children in the Mombasa area with *P. falciparum* parasitaemia were examined and randomly assigned to treatment with one of three antimalarials: amodiaquine, sulfadoxine-pyrimethamine or sulfalene-pyrimethamine. Successfully treated children cleared their parasitemia with mean clearance rates of 2.05; 1.86; and 2.05 days for amodiaquine, sulfadoxine-pyrimethamine and sulfalene-pyrimethamine respectively. Even though, no difference in the effectiveness between the amodiaquine, sulfadoxine-pyrimethamine and sulfalene-pyrimethamine was found, reinfection rates as depicted by day 28 parasitemia differed - amodiaquine 16%; sulfadoxine-pyrimethamine 0%; and sulfalene-pyrimethamine 4.35% (Hagos et al., 1993).

According to a study done in 1992 on children under 5 years in Siaya District Hospital, treatment of malaria with chloroquine was associated with a 33% case fatality rate compared with 11% for children treated with sulfadoxine-pyrimethamine (Zucker, personal communication).

### 1.2.5 Adverse skin reactions due to sulfadoxine-pyrimethamine

With the increase of drug resistance in *P. falciparum*, the efficacy of chloroquine when used for prophylaxis and therapy has become increasingly unreliable (WHO, 1990). Sulfonamide drugs in synergistic combination with dihydrofolate reductase inhibitors (DHFRI) have been shown to be prophylactically and therapeutically effective (Peters, 1987). The most widely used, sulfadoxine-
Pyrimethamine has limited prophylactic and therapeutic application because of the risk of serious skin reactions (Peto and Gilks, 1986; Phillips-Howard and Bjorkman, 1990). The most frequent and serious side effects associated with sulfadoxine-pyrimethamine involve the skin and mucous membranes. The skin rashes can be urticarial, erythematous, maculopapular, morbilliform or purpuric. A severe but fortunately rare adverse effect is the Stevens-Johnson syndrome, consisting of fever, sore throat, chest pains, arthralgia and a variety of skin or mucous membrane lesions occasionally followed by toxic epidermal necrolysis, in which large blisters form. These reactions are caused by the sulfonamide component (Hornstein and Ruprecht, 1982; Olsen et al., 1982; Whitfield, 1982).

Internationally, reported estimates of rates of serious cutaneous reactions to sulfadoxine-pyrimethamine when used for prophylaxis have varied substantially ranging from 1:150 000 users in Switzerland (Steffen and Somain, 1986), 1:5000-8000 users in USA (Miller et al., 1986), 1:10 000 users in Sweden (Hellgren et al., 1987) and 1:2600-10800 in the United Kingdom (Phillips-Howard and West, 1990).

Severe skin reactions are rare when sulfadoxine-pyrimethamine is used for malaria treatment. Twelve cases of skin events related to sulfadoxine-pyrimethamine treatment have been reported to the manufacturers, Roche, since 1984, none had received the recommended single dose therapy (F. Hoffman La-Roche, personal communication). A case of a child who suffered from Stevens-Johnson syndrome was reported by Phillips-Howard et al. (1989).

Adverse reactions to antimalarial drugs are an increasingly important determinant of drug use, as new drugs are introduced into operational use and when antimalarials are used in combination or by persons taking other medications. Appropriate and simplified surveillance systems should be devised specifically for the early detection of adverse reactions occurring in malaria control activities. Such
early detection should be concentrated in settings where new drugs are being used on a wide scale, or where there is a new application (dose, dosage form, combination) of an existing drug.

1.3.0 RATIONALE

Malaria transmission is extremely intense in Kisumu District (a minimum of 1 infective bite every 6 days per person per year and 200-300 infected bites per person per year) (Beier et al., 1988; 1990). The predominant malaria vector is Anopheles gambiae. P. falciparum is the predominant parasite, accounting for more than 85% of infections. Malaria transmission occurs throughout the year, with the peak transmission associated with the two rainy seasons. The "long" rains from March through June produce intense malaria from May through July; the "short" rains of September through October produce another peak transmission from October through November.

Communities in malarious areas of western Kenya frequently treat febrile disease episodes, with over-the-counter medication (Ruebush et al., 1995). Due to the high prevalence of malaria in these communities, antimalarial drugs are frequently sought. With the increasing problem of chloroquine resistance, treatment with alternative drugs such as sulfadoxine-pyrimethamine is becoming common. One of the side effects associated with the use of this drug are severe skin reactions. According to the Kenya Ministry of Health Action Plan for Malaria Control of 1992, a new national policy for malaria treatment with sulfadoxine-pyrimethamine rather than chloroquine, which is now largely ineffective in Kenya, is to be implemented. This study will therefore provide important baseline information on skin reactions associated with sulfadoxine-pyrimethamine before the new national policy on the use of this drug for malaria treatment is implemented.
1.4.0 OBJECTIVES OF THE STUDY

1.4.1 To collect baseline data on number, gender and age of persons with skin rashes presenting to the outpatient and inpatient wards of Kisumu District and New Nyanza Provincial General Hospitals.

1.4.2 To collect data on the spectrum of skin rashes and corresponding prevalence of reported antimalarial drug use in a sample of persons of hospital patients.

1.4.3 To relate use of sulfadoxine-pyrimethamine to the diagnostic categories of skin reactions.
CHAPTER TWO
MATERIALS AND METHODS

2.1 STUDY SITE

The study was conducted in Kisumu District and New Nyanza Provincial General Hospitals (the latter is a provincial-level referral hospital operated by the Kenya Ministry of Health). These hospitals are located within Kisumu town, the third largest town in Kenya, situated on the eastern shores of Lake Victoria in western Kenya. Kisumu town has a population of about 300,000 people. The town lies at latitude 0° 65' south, longitude 34° 48' east and is 3,750 feet above sea level. The local inhabitants are mainly members of the Luo tribe. Their principal occupations are subsistence farming, fishing and cattle rearing.

Within Kisumu town there are 5 government dispensaries, 10 municipal council dispensaries, 2 non-governmental organization dispensaries and an estimated 12 private clinics. Bed capacity for Kisumu District Hospital and New Nyanza Provincial General Hospital is 185 and 302, respectively. In the two hospitals, treatment involves cost sharing and shortages of medicines are common. Within Kisumu town, there are several pharmacies. Chloroquine is inexpensive and is available under various brand names e.g. Malaraquin, Homaquin and Comaquin in pharmacies. Self-treatment with chloroquine is extremely common in western Kenya (Ruebush et al., 1995). Although 50% of *P. falciparum* in western Kenya is resistant to chloroquine at the RII level and 60% of the children continue to experience fever after treatment with the drug, it is the common antimalarial drug stocked in most health centers and hospitals (Bloland et al., 1993).
2.2 RETROSPECTIVE STUDY

A retrospective study was carried out to obtain baseline data on the number, gender and age of persons with skin rashes presenting to the outpatient and inpatient department wards of Kisumu District and New Nyanza Provincial General Hospitals.

Hospital medical records for children and adults outpatient and inpatient departments were considered. Records between April 1994 to March 1995 were retrieved from the Records Department of Kisumu District and the skin clinic in the New Nyanza Provincial General Hospitals respectively. The officer in-charge of the medical records reported that the International Classification of Diseases coding system for specific diagnoses is not used in the two hospitals. For this study, the coding sheet and codes were devised for the investigations as shown in Appendices 1 and 2. The information collected included: location, Patient's name, number, age, gender and diagnosis (see Appendix 3). Skin disorders were classified into ten main categories as follows:

Category 1: Allergy

Category 2: Bacterial infections - Boils, cellulitis, leprosy, pyomyositis, erysipella, stomatitis (glossitis), impetigo, folliculitis, carbuncles and furunculosis.

Category 3: Dermatitis.

Category 4: Drug reactions - Fixed drug eruptions and Stevens-Johnson syndrome.

Category 5: Eczema.

Category 6: Fungal infections - Tinea, candidiasis and pityriasis.

Category 7: Parasitic infections - Scabies, guinea worm, larva migrans and urticaria.

Category 8: Trauma - Burns, ulcers, cuts, bites: (dog, cat, snake, insect and leopard), and wounds.

Category 9: Viral infections - Chickenpox, herpes simplex, herpes zoster, measles and warts.
Category 10: Others - Rashes, birthmarks, hyperkeratosis, vitiligo, leucoderma, hyperpigmentation, psoriasis, lichen, alopecia, acne vulgaris, lupus, scleroderma, pellagra, Kaposi's sarcoma, squamous cell carcinoma, keloids, skin cancers and pemphigus.

2.3 PROSPECTIVE STUDY

A prospective study was carried out to obtain data on: 1) the spectrum of skin rashes and prevalence of reported antimalarial drugs and 2) the diagnostic categories of skin reactions associated with sulfadoxine-pyrimethamine.

2.3.1 Study population

(I) Age and sex

The desired population for the study were children and adults of both sexes. Patients less than 15 years of age were considered children while those older than 15 years were considered adults. Patients ages ranged from 1-57 years with the median age being 25 years.

(ii) The criteria for inclusion of subjects

Any patient with a history of drug-induced skin reaction and who agreed to participate was considered eligible for enrolment in the study. Children were eligible for enrolment in the study when either the parent or guardian consented.

2.3.2 SAMPLE SIZE DETERMINATION

The sample size was dictated by time and willingness to participate in the study. Out of the 40 patients who presented with drug-induced skin reactions, only 33 fulfilled the inclusion criteria and were enrolled in the study. National ethical clearance was not considered necessary for the study.
2.3.3 PROCEDURES

(i) Patient enrolment

Patients presenting with skin features such as rashes (macules maculo-papules and papules), blisters (bullae and skin peeling) and with purpuric reactions (ecchymises, petechia and oozing from membranes) were enrolled in the study. Dermatologic diagnosis of each patient was made by the hospital dermatologist (see Appendix 5). Informed consent was administered after the patient had consented to participate in the study (see Appendix 4).

(ii) Informed consent

Each adult patient who was eligible for the study was informed about the reason for the study and the benefits of the study. Each activity and requirement of the study was explained to the patient. It was clearly communicated that participation in the study was voluntary and that a participant could withdraw from the study at any time without any penalty. The patient was asked if he/she was interested in participating and willing to follow through all the procedures for the investigation (including dermatologic diagnosis and urine collection).

An informed consent form was signed or thumb-printed for documentation of willingness to participate. If the patient did not have authority to grant permission to participate in the study he/she was considered ineligible for enrolment. Fully informed consent was obtained from a parent or guardian of all children enrolled (see Appendix 5).

(iii) Confidentiality

No study participant was identified by name and all personal identifiers were removed from the data when entered into the computer.
2.3.4 LABORATORY STUDIES

(i) Urine collection

Five to ten ml of urine were collected from 30 patients and examined for the presence of chloroquine and sulfadoxine-pyrimethamine. Samples were not collected from 2 patients while one sample was lost in the laboratory.

(ii) Urine analysis

Urine samples were tested for chloroquine using a modified version of the Saker-Solomons test (Mount et al., 1989). The outline of the procedure was as follows: Four standard and 4 study specimen tubes were labelled with the corresponding study number of the patient. Buffer and tetrabromophenolphthalein ethyl ester were pipetted into each study specimen and standard tube. Urine negative for chloroquine was pipetted into each standard tube. Urine from the patient was pipetted into each study specimen tube. Chloroquine standard solution was added into each standard tube. Green or yellow colour indicated the absence of chloroquine while a purple colour indicated the presence of chloroquine. The details of reagent preparation and procedure are shown in Appendix 6.

Urine was tested for sulfadoxine-pyrimethamine using the Bratton-Marshall technique (Almeida-Filho and Souza, 1983). The outline of the procedure was as follows: Four standard and 4 study specimen vials were labelled with the corresponding study number of the patient. Buffer and dimethylaminocinnamaldehyde were added into each standard and study specimen vial. Urine negative for sulfadoxine was pipetted into each standard vial. Urine specimen from the patient was added into each study specimen vial. Ethyl acetate and silicon antiform were added into each standard and study specimen vial. Formation of a ring of bright red colour at the top of the vial indicated the presence of sulfadoxine in the urine. The details of reagent preparation and procedure are shown in Appendix 7.
2.4 DATA STORAGE AND STATISTICAL ANALYSIS

Data were stored using Epilinfo 5 database management system. After entry, the contents of computer files were double-checked against the original data sheets and any errors or omissions were corrected. Data analysis was done by applying the Epilinfo 5 computer package. The significance of differences between means was assessed by the Chi-square ($X^2$) test. The $X^2$ test with a p-value less than 0.05 was considered to be statistically significant.
CHAPTER THREE

RESULTS

3.1 Retrospective study

3.1.1 Kisumu District Hospital

Overall, during the 12-month investigations, a total of 35,950 medical records were documented in both the outpatient and inpatient wards of Kisumu District Hospital. Of this number, only a small proportion (3056, representing only 9.0%) were patients diagnosed with skin events and the rest (32894 or 91.0%) were patients diagnosed as having other medical problems. No cases of drug-induced skin reactions were diagnosed in this population during this period.

(i) Skin disorders by location, gender and age.

From Table I, it is evident that outpatient wards had more reported skin events (2683 or 87.8%) as compared to inpatient wards (373 or 12.2%). Trauma, followed by bacterial infections were the most frequently reported skin events, while dermatitis and eczema were the least reported skin events in all locations.

Generally, skin events were reported more in males than in females but the difference was not significant ($\chi^2=1.72$). In both sexes, trauma followed by bacterial infections were the most frequently reported skin events while dermatitis registered less and eczema the least reported (Table 1).

Adults had more reported skin events than children but the difference was not significant ($\chi^2=10.3$). All categories of skin disorders with the exception of eczema were diagnosed from the age group 5-15 years (Table 2).

From Table 3, for individuals reported with age missing, it is evident that in total trauma, followed by viral and fungal infections were the most frequently reported skin events in both outpatient and
inpatient departments while dermatitis, bacterial infections, eczema and parasitic infections were the least reported skin events.

3.1.2 New Nyanza Provincial General Hospital

In New Nyanza Provincial General Hospital, all the reported cases of skin events were only in the outpatient skin clinic. During the 12-month period covered, only 1,525 medical records (1,557 skin events) were documented as compared to 3,056 in Kisumu District Hospital. The difference between the total number of medical records and the skin events in New Nyanza Provincial General Hospital was due to the fact that some (32) patients had more than one skin event. Of all the documented skin events, drug-induced skin reactions constituted only 1.0% (16 cases).

(i) Skin disorders by location, gender and age

When gender was considered, it was observed that although the incidence of specific disorders differed more or less in males and females, the overall picture seemed to reveal about an equal number of skin events in both sexes ($X^2=0.0$). In complete contrast to the observations made from Kisumu District Hospital, eczema followed by fungal infections were the most frequently reported skin events in both males and females in New Nyanza Provincial General Hospital, while drug reactions were less and trauma the least reported skin events (Table 4).

In terms of age, skin events were more commonly reported in adults than in children. Eczema was the most frequently reported skin event in both adults and children. Parasitic and fungal infections took second and third positions respectively in children. The least reported skin events were trauma in adults and drug reactions, trauma and allergy in children (Table 5). In individuals with the age missing, eczema followed by parasitic infections were the most frequently reported skin events while bacterial and viral infections registered less and trauma the least reported skin events (Table 6).
(ii) Skin reactions to drugs by age and gender

From Table 7, it is evident that Fixed drug eruptions and Stevens-Johnson syndrome were the only cases of drug reactions documented and with very low incidences, being more commonly in adults than in children. The only case of Stevens-Johnson syndrome was reported from an adult patient.

Generally, males had more reported cases of drug reactions than females but the difference was not significant (X2=0.0). The only case of Stevens-Johnson syndrome was diagnosed in a male patient (Table 8).

3.2 Prospective study

(i) Study population

The 12-month study was conducted on the 33 out of 40 patients who fulfilled the inclusion criteria (17 males and 16 females). Of the 33 patients, 32 were from Kisumu District Hospital and 1 was from New Nyanza Provincial General Hospital.

Ten of the 33 patients had sulfadoxine-pyrimethamine minor skin reactions (Table 11). Of the 10 patients, 3 were males and 7 were females. Nine of the 10 patients were adults and the child was 1 year old. Twenty-one of the 30 urine samples were positive for the antimalarial drugs tested. Twelve (57%) of these were positive for sulfadoxine-pyrimethamine, 5 (24%) for sulfadoxine-pyrimethamine and chloroquine and 4 (19%) for chloroquine.

(ii) Skin reactions to sulfadoxine-pyrimethamine and other drugs by body parts first affected and signs experienced

The most frequently affected parts were the face followed by the limbs while the neck and the lips were the parts least affected by sulfadoxine-pyrimethamine and other drugs taken (Table 9). At the onset of skin reactions, fever, weakness, cough and sore throat were the most frequent signs experienced by the patients who had taken sulfadoxine-pyrimethamine (Table 10).
(iii) Sulfadoxine-pyrimethamine induced skin reactions by categories

Of the 5 types of drug-induced skin reactions described, Rashes followed by Toxic epidermal necrolysis were the most frequently diagnosed skin reactions while Papular urticaria followed by Fixed drug eruptions were the least (Table 11).

A total of nine drugs reportedly taken were found to have induced skin reactions. Sulfadoxine-pyrimethamine constituted 10 cases of minor skin reactions. Eleven cases of skin reactions to thiacetazone were reported. Seven of the reactions to thiacetazone were severe viz.: four cases of Toxic epidermal necrolysis and three of Stevens-Johnson syndrome (Table 11).

(iv) Sulfadoxine-pyrimethamine induced skin reactions by risk factors

Skin reactions were more frequently reported in adults than in children. The dose of sulfadoxine-pyrimethamine taken varied, for adults one dose was 3 tablets and for children half a dose was one and ahalf tablets. The time lapse between drug intake and onset of skin reactions varied, in adults it was one week and in children it was less than a week. Two of the 9 adult patients had a history of previous skin reactions to sulfadoxine-pyrimethamine.
### TABLE I.

Number of reported skin disorders by location from Kisumu District Hospital

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Trauma</td>
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<td>1242</td>
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<td>28</td>
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<td>117</td>
<td>1207</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>176</td>
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<td>28</td>
<td>57</td>
<td>180</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>2</td>
<td>5</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fung. Infec.</td>
<td>Outpatient</td>
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<td>47</td>
<td>86</td>
<td>50</td>
<td>183</td>
<td>17</td>
<td>5</td>
<td>9</td>
<td>31</td>
<td>155</td>
<td>214</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paras. Infec.</td>
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<td></td>
<td>65</td>
<td>43</td>
<td>47</td>
<td>155</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>112</td>
<td>164</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Outpatient</td>
<td></td>
<td>24</td>
<td>19</td>
<td>47</td>
<td>90</td>
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<td>0</td>
<td>2</td>
<td>7</td>
<td>48</td>
<td>97</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>12</td>
<td>15</td>
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<td>1</td>
<td>4</td>
<td>30</td>
<td>46</td>
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<tr>
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<td></td>
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<td></td>
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<tr>
<td>Others</td>
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<td>30</td>
<td>32</td>
<td>92</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>65</td>
<td>99</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>1351</td>
<td>878</td>
<td>454</td>
<td>2683</td>
<td>144</td>
<td>101</td>
<td>128</td>
<td>373</td>
<td>2474</td>
<td>3056</td>
</tr>
</tbody>
</table>

Sample size (n) = 3,056 skin disorders.
TABLE 2.
Number of reported skin disorders by age from Kisumu District Hospital.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Age (years)</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5</td>
<td>5-15</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Trauma</td>
<td>136</td>
<td>370</td>
<td>778</td>
</tr>
<tr>
<td>Bac. Infec</td>
<td>82</td>
<td>50</td>
<td>495</td>
</tr>
<tr>
<td>Viral Infec</td>
<td>43</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Allergy</td>
<td>19</td>
<td>30</td>
<td>156</td>
</tr>
<tr>
<td>Fungal Infec</td>
<td>53</td>
<td>19</td>
<td>131</td>
</tr>
<tr>
<td>Paras. Infec</td>
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<td>50</td>
<td>64</td>
</tr>
<tr>
<td>Dermatitis</td>
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<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Eczema</td>
<td>14</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Others</td>
<td>35</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>482</td>
<td>576</td>
<td>1880</td>
</tr>
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</table>

Sample size (n)= 3,056 skin disorders.
TABLE 3.
Number of reported individuals with age missing by location and gender from Kisumu District Hospital.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Outpatient</th>
<th></th>
<th>Inpatient</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ma  Fe</td>
<td>Ma  Fe</td>
<td>Ma  Fe</td>
<td>Ma  Fe</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>19  15</td>
<td>12  13</td>
<td>0  10</td>
<td>6  0</td>
<td>75</td>
</tr>
<tr>
<td>Bac infections</td>
<td>0  0</td>
<td>1  0</td>
<td>1  0</td>
<td>1  0</td>
<td>3</td>
</tr>
<tr>
<td>Viral Infections</td>
<td>5  0</td>
<td>0  3</td>
<td>2  1</td>
<td>0  0</td>
<td>11</td>
</tr>
<tr>
<td>Allergy</td>
<td>0  4</td>
<td>2  0</td>
<td>0  0</td>
<td>2  1</td>
<td>9</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>2  0</td>
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<td>11</td>
</tr>
<tr>
<td>Para. infections</td>
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<tr>
<td>Dermatitis</td>
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<td>0  1</td>
<td>0  0</td>
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<tr>
<td>Others</td>
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<td>0  0</td>
<td>0  0</td>
<td>1  0</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17  32</td>
<td>16  21</td>
<td>5  14</td>
<td>11  2</td>
<td>118</td>
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Sample size (n) = 118 individuals reported with age missing.
TABLE 4

Number of reported skin disorders by gender from New Nyanza Provincial General Hospital.

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<th>Disorder</th>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td>Trauma</td>
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<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Bact. infect</td>
<td>10</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>Viral infections</td>
<td>32</td>
<td>33</td>
<td>65</td>
</tr>
<tr>
<td>Allergy</td>
<td>27</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>Fungal infections</td>
<td>86</td>
<td>106</td>
<td>192</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>77</td>
<td>57</td>
<td>134</td>
</tr>
<tr>
<td>Parasitic infec.</td>
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<td>154</td>
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<tr>
<td>Eczema</td>
<td>234</td>
<td>262</td>
<td>496</td>
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<tr>
<td>Drugs reactions</td>
<td>9</td>
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<td>16</td>
</tr>
<tr>
<td>Others</td>
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<td>188</td>
<td>402</td>
</tr>
<tr>
<td>Total</td>
<td>775</td>
<td>782</td>
<td>1557</td>
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</table>

Sample size (n)= 1557 skin disorders.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>0-5</th>
<th>5-15</th>
<th>&gt; 15</th>
<th>Age missing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Bac.infec.</td>
<td>2</td>
<td>2</td>
<td>25</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>Viral infe</td>
<td>3</td>
<td>8</td>
<td>47</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>Allergy</td>
<td>3</td>
<td>1</td>
<td>36</td>
<td>7</td>
<td>49</td>
</tr>
<tr>
<td>Fungal infec.</td>
<td>20</td>
<td>23</td>
<td>136</td>
<td>13</td>
<td>192</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>7</td>
<td>6</td>
<td>109</td>
<td>12</td>
<td>134</td>
</tr>
<tr>
<td>Paras. infec.</td>
<td>35</td>
<td>13</td>
<td>87</td>
<td>19</td>
<td>154</td>
</tr>
<tr>
<td>Eczema</td>
<td>122</td>
<td>49</td>
<td>259</td>
<td>66</td>
<td>496</td>
</tr>
<tr>
<td>Drug reactions</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Others</td>
<td>33</td>
<td>46</td>
<td>276</td>
<td>47</td>
<td>403</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>238</td>
<td>151</td>
<td>1002</td>
<td>176</td>
<td>1557</td>
</tr>
</tbody>
</table>

Sample size (n) = 1557 skin disorders.
TABLE 6

Number of reported individuals with age missing by gender from New Nyanza General Provincial Hospital.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Adults</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infections</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal infections</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>9</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Para infections</td>
<td>7</td>
<td>10</td>
<td>0</td>
<td>5</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>25</td>
<td>9</td>
<td>4</td>
<td>28</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Reactions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>9</td>
<td>11</td>
<td>20</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>55</td>
<td>36</td>
<td>27</td>
<td>58</td>
<td>176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sample size (n)= 176 individuals reported with age missing.
Table 7

Number of reported drug-induced skin reactions by age from New Nyanza Provincial General Hospital

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Age (Years)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5</td>
<td>5-15</td>
</tr>
<tr>
<td>Fixed drug eruptions</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Sample size (n)=16 drug reactions.
### Table 8

Number of reported drug-induced skin reactions by gender from New Nyanza Provincial General Hospital

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed drug eruptions</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7</td>
<td>9</td>
<td>16</td>
</tr>
</tbody>
</table>

Sample size (n)=16 drug reactions.
### Table 9

Body parts first affected at the onset of drug-induced skin reactions

<table>
<thead>
<tr>
<th>Body part</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Limbs</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Trunk</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>All over</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neck</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lips</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>5</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

**KEY:**

A = Chloroquine/sulfadoxine-pyrimethamine/penicillin  
B = Sulfadoxine-pyrimethamine/penicillin  
C = Sulfadoxine-pyrimethamine  
D = Trimethoprim-sulfamethoxazole  
E = Thiacetzone  
F = Sulfadoxine-pyrimethamine/chloroquine  
G = Chloramphenicol  
H = Sulfadoxine-pyrimethamine/trimethoprim-sulfamethoxazole  
J = Chloroquine/trimethoprim-sulfamethoxazole

**NOTE:**

1. Sulfadoxine-pyrimethamine and chloroquine are anti-malarial drugs, penicillin and trimethoprim-sulfamethoxazole are anti-biotics, chloramphenicol is anti-bacterial and thiacetzone is an anti-tuberculosis drug.
2. Drug combinations were either prescribed by the Doctor or Clinical Officer or over the counter.
### TABLE 10

Signs observed at the onset of drug-induced skin reactions

<table>
<thead>
<tr>
<th>Sign</th>
<th>Drug taken</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weakness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Itching</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**KEY:**

A = Chloroquine/sulfadoxine-pyrimethamine/penicillin  
B = Sulfadoxine-pyrimethamine/penicillin  
C = Sulfadoxine-pyrimethamine  
D = Trimethoprim-sulfamethoxazole  
E = Thiacetazone  
F = Sulfadoxine-pyrimethamine/chloroquine  
G = Chloramphenicol  
H = Sulfadoxine-pyrimethamine/trimethoprim-sulfamethoxazole  
J = Chloroquine/trimethoprim-sulfamethoxazole
TABLE 1  

Drugs reported taken and accompanying skin reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>J</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>PU</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>FDE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SJS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TEN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

**KEY:**

- **PU** = Papular urticaria
- **FDE** = Fixed drug eruptions
- **SJS** = Stevens-Johnson syndrome
- **TEN** = Toxic epidermal necrolysis
- **A** = Sulfadoxine-pyrimethamine
- **B** = Sulfadoxine-pyrimethamine/chloroquine
- **C** = Sulfadoxine-pyrimethamine/penicillin
- **D** = Chloroquine/sulfadoxine-pyrimethamine/penicillin
- **E** = Trimethoprim-sulfamethoxazole
- **F** = Thiacetazone
- **G** = Chloramphenicol
- **H** = Sulfadoxine-pyrimethamine/trimethoprim-sulfamethoxazole
- **J** = Trimethoprim-sulfamethoxazole/chloroquine
4.1 DISCUSSION

Only a few antimalarial drugs effectively treat drug-resistant malaria infections. When serious safety issues arise therefore, a thorough examination of the risk associated with the suspect drug, in relation to its advantages, before being considered as a first line therapy for malaria.

In the past few years a number of safety issues have arisen on most of the antimalarials available. One of the most pressing of these is the reported adverse skin reactions to sulfadoxine-pyrimethamine. Other safety issues which appear less significant but which may have logistical impact on policy recommendations is the putative interrelationship between HIV and sulfadoxine-pyrimethamine use. Sulfadoxine-pyrimethamine when used for malaria treatment in HIV positive individuals has been reported to cause adverse skin reactions (WHO, 1990). The documented interrelationship between HIV and sulfadoxine-pyrimethamine use could not be established in this study because no HIV tests were performed on the patients with sulfadoxine-pyrimethamine induced skin reactions. In this study, it was hypothesized that sulfadoxine-pyrimethamine is associated with adverse skin reactions when used for malaria treatment in an area with high transmission of chloroquine-resistant P. falciparum. The results showed that sulfadoxine-pyrimethamine was only associated with minor skin reactions in the form of rashes (Table 11). But since reactions to sulfadoxine-pyrimethamine are rare according to previous reports, the sample size of this study may also have affected the results in that only extremely common reactions to sulfadoxine-pyrimethamine would have been detected.

Severe skin reactions like Stevens-Johnson syndrome and Toxic Epidermal necrolysis were not seen associated with sulfadoxine-pyrimethamine use but rather in patients on thiacetazone for tuberculosis treatment. Since urine analysis was limited only to testing for sulfadoxine-pyrimethamine
and chloroquine in this study, a clear causal relationship between the severe skin reactions noted and thiacezone could not be established.

Generally, sulfadoxine-pyrimethamine induced skin reactions have been associated with risk factors such as age, dose taken, the time lapse between drug intake and onset of skin reactions; and previous exposure to the drug (Bjorkman and Phillips-Howard, 1991). Sulfadoxine-pyrimethamine skin reactions are more common in adults than in children (Bottiger, 1979). In the 1979 study, adults had more reported cases of sulfadoxine-pyrimethamine skin reactions than children. This was confirmed in the current study i.e. 9 adults and 1 child had minor skin reactions associated with sulfadoxine-pyrimethamine. The reasons for this might be that sulfadoxine-pyrimethamine is used a lot more by the parents or due to failure by the parents to take children for medical treatment because the hospital may too far away. Failure of treatment in children could also be due to inadequate dosage (i.e. the drug may not be completely absorbed e.g. because of vomiting). On the other hand, adults may have been previously exposed to the drug.

The doubling of a dose in adults during clinical trial has been reported to have a significant effect upon the incidence of adverse skin reactions (Bjorkman and Phillips-Howard, 1991). Previously sensitized individuals overreact to sulfadoxine-pyrimethamine (Hellgren, 1987). Sulfadoxine, the sulfonamide component of sulfadoxine-pyrimethamine, has an extremely long half-life of 7-9 days. Drugs with a long half-life like trimethoprim-sulfamethoxazole and sulfadoxine-pyrimethamine have been documented to cause adverse skin reactions (Bjorkman and Phillips-Howard, 1991). The time lapse between sulfadoxine-pyrimethamine intake and onset of skin reactions is an important determinant of the severity of adverse skin reactions. Indeed, among severe reactions to sulfadoxine-pyrimethamine, a small cluster occurs within 1-3 days in previously sensitized individuals; then a large
cluster develops after 1-9 weeks (Hellgren, 1987; Bjorkman and Phillips-Howard, 1991). From this study, only 2 patients had a history of previous skin reaction to sulfadoxine-pyrimethamine and it occurred within one week after treatment. The 2 patients had minor skin reactions in form of rashes and were reported to have taken sulfadoxine-pyrimethamine alone.

Although sulfadoxine-pyrimethamine has been associated with severe, occasionally fatal skin reactions, these reactions have occurred primarily among people taking the drug for chemoprophylaxis. The frequency and severity of adverse skin reactions associated with sulfadoxine-pyrimethamine correlate with the dose and duration of use (Bjorkman and Phillips-Howard, 1991). Little data is available on adverse skin reactions following single dose treatment with sulfadoxine-pyrimethamine. Single dose treatment with sulfadoxine-pyrimethamine was estimated to have a 40-fold lower risk of adverse skin reactions compared with weekly chemoprophylaxis (Sturchler et al., 1993).

It is common knowledge that chloroquine has been rendered almost useless through problems of drug resistance partially resulting from inappropriate and irrational use of the drug. Adopting sulfadoxine-pyrimethamine as the first-line treatment of malaria, and potentially of all fevers, in areas of chloroquine-resistant *P. falciparum* could markedly increase its use. The widespread use of sulfadoxine-pyrimethamine might increase the occurrence of severe skin reactions (Bjorkman and Phillips-Howard, 1991). In addition, the increased use of this drug could potentially select for local isolates of *P. falciparum* resistant to sulfadoxine-pyrimethamine (Watt and Shanks, 1991). When sulfadoxine-pyrimethamine is used as first-line treatment for *P. falciparum*, surveillance methods for monitoring adverse skin reactions to the drug are essential. The second question apart from potential adverse side effect, that is often raised regarding proposals to change first-line treatment from chloroquine to sulfadoxine-pyrimethamine for *falciparum* malaria in Africa concern cost. Price estimates for sulfadoxine-pyrimethamine in Kenya (about one US $ per tablet) as compared to Malawi
(two US$ equivalent to Ksh 60 per tablet) (Foster, 1991) suggest a dose of sulfadoxine-pyrimethamine can be near or below that of chloroquine (0.5 US$ equivalent Ksh 35 per tablet).

From the retrospective study, only 16 out of 1,557 cases of drug induced skin reactions were documented (Table 4). This might be due to the fact that these reactions rarely occur. No drugs were incriminated for these reactions. Outpatient wards had more reported cases of skin events than inpatient wards. This might be due to the fact that skin disorders rarely require medical admission.

Severe skin reactions are rare disorders, for which a measurement of risk usually requires a large study population and long periods of observations for definitive results (WHO, 1990). For this study to be conclusive, a sample size of 100-200 patients would have been adequate. In the current study, the sample size in the prospective portion was dictated by time (limited to one year) and therefore it was difficult to determine whether the use of sulfadoxine-pyrimethamine was increasing and whether the occurrence of adverse skin reactions due to this drug are likely to increase. Another limitation of the prospective study was probably under-reporting or non-reporting of drug induced-skin reactions. Under-reporting would occur when either the patient or doctor fails to recognize or to report the condition. Non-reporting by the doctor may result because of ignorance of the severity of the case or of the necessity to report or fear (and maybe guilt) of the patient's reaction to the mode of treatment. A major source of difficulty in carrying out the study was to maintain follow-up of patients in order to establish the outcome of sulfadoxine-pyrimethamine skin reactions. In the current study, periodic home and hospital visits were adapted for establishing the outcome skin reactions.

Other drugs like amodiaquine, halofantrine and quinine are all efficacious in the treatment of uncomplicated malaria in Kenya (MoH, 1992). However, amodiaquine when used for treatment has severe liver side effects. Halofantrine has severe cardiac side effects and additionally is too expensive.
to be recommended for general use. Parenteral quinine is reserved for severe malaria. Taking into consideration the above mentioned side effects of drugs such as amodiaquine and halofantrine, the restrictions on quinine usage and the fact that sulfadoxine-pyrimethamine has been documented to cause adverse skin reactions only during chemoprophylaxis, but rarely during treatment (Bjorkman and Phillips-Howard, 1991), the minor skin reactions to sulfadoxine-pyrimethamine observed in this study suggest that it may be safely used for the treatment of chloroquine-resistant *falciparum* malaria.

In conclusion, sulfadoxine-pyrimethamine may be used as a first-line treatment of malaria, as long as surveillance is maintained to monitor any adverse skin reactions by cooperation between the providers of health facilities, health practitioners and the patients.

4.2 SUMMARY OF FINDINGS AND RECOMMENDATIONS

1. Sulfadoxine-pyrimethamine can be used for treatment of chloroquine-resistant *falciparum* malaria.
2. Sulfadoxine-pyrimethamine skin reactions are minor and not a public health problem.
3. Age is a risk factor for sulfadoxine-pyrimethamine skin reactions.
4. Prospective study is useful in monitoring skin reactions to sulfadoxine-pyrimethamine.
5. Surveillance for adverse reactions to antimalarial drugs is needed.
6. Monitoring of drug resistance and evaluation of alternative drugs and regimens is needed.
7. There is a need for clinical studies to assess the safety of sulfadoxine-pyrimethamine in HIV positive patients.
REFERENCES


APPENDICES

APPENDIX 1

SKIN RASH STUDY-KISUMU DISTRICT HOSPITAL

CODING SHEET FOR ALL DIAGNOSES

01 Malaria (clinical/chronic)
02 Anaemia
03 Fever
04 Splenomegaly (enlarged spleen)
05 Malnutrition - Marasmus/kwashiorkor/caloric malnutrition
06 Measles
07 Polio
08 Dehydration
09 Acidosis
10 Acute respiratory infection/respiratory tract infection/sinusitis
11 Pneumonia (bronchopneumonia)
12 Bronchitis
13 Otitis
14 Mastoiditis
15 Cough
16 Asthma/bronchial constriction/bronchial spasm
17 Bronchiolitis
18 Whooping cough/Pertussis
19 Jaundice/hepatitis/haemolytic jaundice/liver cirrhosis
20 Vomiting/diarrhoea/gastroenteritis/haemophysis
21 Hernia
22 Cholera
23 Ascariasis/intestinal helminths/hookworm
24 Amebiasis (Amoebic dysentery)/dysentery/giardiasis/shigellosis
25 Gastritis
26 Inguinal hernia
27 Dyspepsia/peptic ulcer disease/hiccup
28 Abdominal mass
29 Intestinal obstruction/pyloric stenosis
30 Skin rash (dermatitis) (septic sores) (eczema) (eczematous bullae) (herpes zoster) (chickenpox)
31 Hydrocephalus
32 Scabies/Infected scabies
33 Burn(s)
34 Trauma-cut/wound/bruise/injury/soreness/fracture/X-ray/road traffic accident/ assault/ soft tissue injury
35 Oedema/ascites/swelling/pleural effusion
36 Boil/abscess
37 Foreign body
38 Oral moniliasis (thrush), any candidiasis
39 Adenitis/swollen glands/mumps/lymphadenitis
40 Tinea capitis (corporis)/ringworm/fungal infection
41 Ulceration/skin ulcer
42 Umbilical infection
43 Tuberculosis/Koch's disease
44 Tumor/cancer/leukemia/Burkitt's lymphoma/Kaposi's sarcoma/ovarian cyst/lipoma
45 Sickle cell disease
46 Nephrotic syndrome/nephritis/glomerulonephritis
47 Congenital malformations
48 Rheumatic fever/Rheumatic heart disease
49 Rabies
50 Sepsis/neonatal sepsis
51 Congestive cardiac failure/hypertension
52 Meningitis
53 Arthritis/septic arthritis/osteomyelitis
54 Urinary tract infection/cystitis/urethritis/pyelonephritis/bubo/granuloma/haematuria/syphilis/paraphysis/phimosis
55 Orchitis (swollen testicle)/hydrocele
56 Convulsions/fits/febrile convulsions/epilepsy
57 Cerebral malaria
58 HIV infection/immunosuppression/AIDS related complications
59 Ophthalmia neonatorum
60 Conjunctivitis/leucoma/staphyloma/style/other eye problems
61 Stomatitis (glossitis)
62 Skin-other/pustules/urticaria/pemphigus/psoriasis/leprosy/squamous cell carcinoma/dandruff/pellagra/pityriasis/impetigo/pyoderma/furuncles/carbuncles/folliculitis/

63 Dental problems/gingivitis

64 Balanitis

65 Tonsillitis/pharyngitis/adenoids

66 Tetanus

67 Aspiration

68 Allergy

69 Abdominal pain/colic/inflammatory bowel syndrome/any pain

70 Poisoning

71 Brain damage (neurological disorder, Bells palsy, coma, myalgia, lumbergo and drowsiness)

72 Hypoglycemia

73 Rectal prolapse/hemorrhoids/pits

74 Epistasis

75 Fainting/syncope/dizziness

76 Shortness of breath/dyspnoea

77 Schistosomiasis/bilharzia

78 Retained placenta

79 Pre-eclampsia
80 Obstetrical problem/hyperemesis/polyhydramnios/oligohydramnios/postmaturity/chancroids
81 Ruptured spleen
82 Pelvic inflammatory disease
83 Abortion-complete
84 Abortion-incomplete
85 Abortion-inevitable
86 Abortion-threatening
87 Vaginal bleeding/dysfunctional uterine bleeding
88 Uterine fibroid
89 Carcinoma of the cervix
90 Gynecology, other (include trichomonas/galactorrhoea
91 Draining liquor/premature rupture of membranes
92 Intrauterine pregnancy
93 In labor (labor pains)
94 Antepartum hemorrhage
95 Postpartum hemorrhage
96 Premature labor
97 Premature delivery
98 Intrauterine fetal death
99 Ectopic pregnancy
100 Tubal ligation
101 Medical, other/anorexia
102 Psychiatry/hysteria/schizophrenia/puerperal psychosis
103 Diabetes mellitus
104 Cellulitis
105 Typhoid/enteric fever/salmonellosis
APPENDIX 2

SKIN RASH STUDY-KISUMU DISTRICT/NYANZA PROVINCIAL HOSPITALS

CODING SHEET FOR SKIN DIAGNOSES

<table>
<thead>
<tr>
<th>Code</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Scabies</td>
</tr>
<tr>
<td>02</td>
<td>Dermatitis</td>
</tr>
<tr>
<td>03</td>
<td>Eczema</td>
</tr>
<tr>
<td>04</td>
<td>Herpes zoster/post-herpetic neuralgia</td>
</tr>
<tr>
<td>05</td>
<td>Herpes simplex</td>
</tr>
<tr>
<td>06</td>
<td>Measles</td>
</tr>
<tr>
<td>07</td>
<td>Boil/abscess</td>
</tr>
<tr>
<td>08</td>
<td>Burns</td>
</tr>
<tr>
<td>09</td>
<td>Tinea (capitis, corporis, pedis)</td>
</tr>
<tr>
<td>10</td>
<td>Chickenpox</td>
</tr>
<tr>
<td>11</td>
<td>Allergy</td>
</tr>
<tr>
<td>12</td>
<td>Skin ulcer/tropical ulcer/ulcer</td>
</tr>
<tr>
<td>13</td>
<td>Urticaria</td>
</tr>
<tr>
<td>14</td>
<td>Heat rash</td>
</tr>
<tr>
<td>15</td>
<td>Kaposis sarcoma</td>
</tr>
<tr>
<td>16</td>
<td>Pemphigus</td>
</tr>
<tr>
<td>17</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>18</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>19</td>
<td>Erythema multiform</td>
</tr>
<tr>
<td>20</td>
<td>Psoriasis</td>
</tr>
</tbody>
</table>
21 Squamous cell carcinoma
22 Leprosy
23 Dandruff
24 Stomatitis/glossitis
25 Pellagra
26 Alopecia/baldness
27 Pityriasis versicolor/alba/rosea
28 Impetigo
29 Fixed drug eruption(s)
30 Pyomyostis
31 Rubella
32 Verruca
33 Other skin cancers
34 Pyoderma/pustules/furuncles/carbuncles/folliculitis
35 Mycoses-candidiasis
36 Viral infections/warts/other viral
37 Cellulitis
38 Lichen
39 Pediculosis/body lice
40 Jiggers/tungiasis
41 Acne vulgaris/pimples
42 Wound/cut/bruise
43 Vitiligo/leucoderma/albino/hyperpigmentation
44 Septic wound/sores/umbilical stump/wound infection
45 Snake bite/dog bite/human bite/leopard bite/cat bite
46 Insect bite
47 Gangrene
48 Erysipella
49 Connective tissue disorders/lupus vulgaris
50 Hyperkeratosis
51 Scleroderma
52 Naevus/birth mark
53 Guinea worm
54 Cutaneous larva migrans/creeping eruption
90 Skin-other (lesions, body rash)
APPENDIX 3: SKIN RASH KISUMU DISTRICT/NYANZA PROVINCIAL HOSPITALS

1. Location: 1) Outpatient male
2) Outpatient female
3) Outpatient pediatric/children
4) Inpatient male
5) Inpatient female
6) Inpatient pediatric/children
7) Outpatient skin clinic

2. Name

3. Number

4. Date seen:

5. Age
   years
   months

6. Sex
   1) Female
   2) Male

7. Diagnosis

8. Skin related? Y/N

9. If skin related then code:
APPENDIX 4: INFORMED CONSENT AGREEMENT

The Kenya Medical Research Institute and the Centers for Disease Control (Atlanta, Georgia, USA) are doing a study on the adverse skin reactions to sulfadoxine-pyrimethamine in order to understand the implications of treatment policies. With the increasing problem of chloroquine resistance, treatment with sulfadoxine-pyrimethamine is becoming more common. Sulfadoxine-pyrimethamine may cause skin rash or sores in the mouth, which can be severe. This may happen in 1 person in 20,000 who receive the drug.

If you agree to participate in these study activities, you can expect the following to occur in relation, to your enrolment:

1. You will be interviewed on the antimalarial drug(s)/other drugs you may have taken.

2. You will be asked to give a urine sample, that will be examined for the presence of any antimalarial drugs you may have taken.

3. All information you provide will be handled in a confidential manner. None of your names will be used in any published report of the results of the study.

Participation in the study is completely voluntary and you may at any time during the course of the study revoke the consent and withdraw from the study without further penalty or loss of benefits.

If there are any questions related to the study, ask the investigator before signing the informed consent.

Thank you very much for your time.

Volunteer's/Parent/Guardian's statement: I acknowledge receipt of this agreement, to include: - the consent explanation and the informed consent agreement.

Volunteer's/Parent/Guardian's signature or thumbprint

Date
Volunteer's/Parent/Guardian's printed name ______________

Witness's statement: I was present during the explanation referred to above, the Volunteer's opportunity for questions, and hereby witness to the volunteer's signature or thumbprint.

Witness's signature or thumbprint ______________

Date ____________

Witness's printed name _____________________

Investigator's signature ______________

Date ____________

Investigator's printed name ______________
APPENDIX 5: SKIN DISORDERS: OPD/IPD REPORT FORM, KISUMU DISTRICT AND NYANZA PROVINCIAL HOSPITALS.

DATE: .../.../... PATIENT CODE ........

HOSPITAL: [ ] Kisumu District [ ] New Nyanza

OPD/IPD: [ ] < 5 Clinic [ ] adults [ ] skin clinic [ ] emergency

OBSERVER: ...........................................

PATIENT NAME: ...........................................

AGE: .../.../... ..........................

Years  Months

SEX: [ ] male [ ] female

ADDRESS: ........................................................................................................

........................................................................................................

HISTORY OF ONSET OF SKIN CONDITION:

DATE OF ONSET: .../.../... 

FIRST SIGNS: where on the body did it first start

[ ] trunk  [ ] face  [ ] limbs  [ ] genitals  [ ] other .................

[ ] all over  [ ] do not remember

OTHER SIGNS: Did any of the following occur at the time of onset

[ ] sore throat  [ ] fever  [ ] cough  [ ] weakness  [ ] other .................

HISTORY: Has the patient had the same skin condition before

[ ] yes: when .................................

[ ] no
EXCLUSION CRITERIA: CLEAR SIGNS OF THE FOLLOWING SKIN CONDITIONS:

- [ ] parasitosis
- [ ] scabies
- [ ] pediculosis
- [ ] pyoderma
- [ ] tropical ulcer
- [ ] wound infection
- [ ] mycoses
- [ ] tinea
- [ ] viral infections
- [ ] measles
- [ ] herpes simplex
- [ ] abscesses
- [ ] facial cellulitis
- [ ] acne vulgaris
- [ ] eczema
- [ ] lichen simplex
- [ ] psoriasis
- [ ] vitiligo
- [ ] leprosy
(2) INCLUSION CRITERIA: ALL PATIENTS WITH SKIN CONDITIONS

Describe presenting skin features:

[ ] rash  [ ] macules (non-palpable change in skin color)
[ ] papules (small circumscribed elevations on skin)
[ ] maculo-papular (macules/raised palpable spots)
[ ] blisters  [ ] bullae (large watery blisters)
[ ] skin blistering and peeling
[ ] purpuric  [ ] ecchymoses (large bruises)
[ ] petechia (small haemorrhagic spots)
[ ] oozying from mucous membranes

DRUG HISTORY: Were any drugs taken before or at the time of onset

[ ] yes  [ ] no

IF YES, WHICH DRUGS WERE TAKEN

[ ] chloroquine  [ ] sulfadoxine-pyrimethamine (Fansidar)
[ ] trimethoprim-sulfamethoxazole (Cotrimoxazole)
[ ] dapsone  [ ] other sulfa drug (.....................)
[ ] thiacetazone  [ ] tetracycline
[ ] penicillin  [ ] erythromycin
[ ] clindamycin  [ ] quinoline
[ ] cephalosporin  [ ] other microbial (.....................)
[ ] anticonvulsant (.....................)
[ ] non-steroidal antiinflammatory drugs
[ ] other antipyretics (.....................)  [ ] other (.....................)
DATE DRUG STARTED ..........
DATE DRUG STOPPED ..........
HAS THE SAME DRUG BEEN TAKEN ON A PREVIOUS OCCASION
[ ] yes [ ] no [ ] do not remember
IF YES, WHEN WAS THIS ..........
ON THIS PREVIOUS OCCASION, DID ANY OF THE FOLLOWING OCCUR
[ ] fever [ ] skin rash [ ] similar skin reaction [ ] other (Describe............)
CURRENT DIAGNOSIS:
- Drug induced reaction [ ] yes [ ] no
- Serious ADR [ ] yes [ ] no
- Diagnostic category ............
- Suspect drug ............
CURRENT TREATMENT/ DRUGS USED FOR TREATMENT OF SKIN CONDITION
DISPOSITION
[ ] Admitted
[ ] outpatient treatment
OUTCOME OF SKIN CONDITION
[ ] Healed Date....../
[ ] Referred Date....../
[ ] Died Date....../
LABORATORY TEST
- Urine sample taken [ ] yes [ ] no
   Results__________________________
APPENDIX 6: Saker-Solomons test for chloroquine in urine

Reagent preparation

1. pH 8 buffer 162 g of Potassium dibasic anhydrous (K₂HPO₄) were mixed with 500 ml of distilled water.

2. Tetrabromophenolphthalein ethyl ester (TBPEE) 12.5 mg of TBPEE were with 25.0 ml of chloroform and 2.5 ml of hydrochloric acid were then added to the mixture of TBPEE and chloroform.

3. Chloroquine standard solution Injectable chloroquine in a 30 ml bottle from a chemist was added to 1 ml distilled water.

Procedure

1. Four standard tubes were labelled as 0, 1, 2, 3 and 4 specimen tubes were labelled with the corresponding study number.

2. 1.0 ml of buffer was pipetted into each standard and specimen tube.

3. 0.2 ml of TBPEE was pipetted into each standard and specimen tube.

4. 2.0 mls of blank urine (negative for chloroquine) were pipetted into standard tubes.

5. 2.0 mls of urine specimen were pipetted into each study specimen tube.

6. 4, 8 and 12 microlitres of chloroquine standard solution were added into the standard tubes 1, 2, and 3 respectively.

7. Tubes were shaken for approximately 30 seconds and left to stand for approximately 10 minutes

8. Green or yellow colour indicated the absence of chloroquine in the urine while a purple colour indicated the presence of chloroquine in the urine.
APPENDIX 7: Sulfadoxine test for sulfadoxine in urine.

Reagent preparation

1. Dimethylyaminocinnamaldehyde (DMACNA) colour reagent
   150.0 mg of DMACNA were mixed with 0.3 ml of 12m (molar) hydrochloric acid and 50.0 ml of methanol

2. pH 5.5 buffer 11.0 g of Potassium dibasic anhydrous (K$_2$HPO$_4$) were mixed with 500 ml distilled water.

3. Silicon antifoam emulsion (SAG-10) 50 ml of SAG-10 emulsion were diluted 50 ml of distilled water.

4. Ethyl Acetate - manufactured by the sigma chemical company of USA. This was bought already prepared.

5. Sulfadoxine standard solution - manufactured by the sigma chemical company of USA. This was bought already prepared.

Procedure

1. 4 standard vials were labelled as 0, 1, 3 and 7 and 4 study specimen vials were labelled with the corresponding study number.

2. 0.5 ml buffer and 0.5 ml dimethylyaminocinnamaldehyde were added into each standard and specimen vial.

3. 2.0 ml of blank urine (negative for sulfadoxine) were added into each standard vial.

4. Into each study specimen vials, 2.0 ml of each corresponding urine sample were added.

5. Standard and study specimen vials were capped and inverted 20 times. After ethyl acetate had risen to the top, one drop of SAG-10 was added into each standard and study specimen vial and swirled gently for a few seconds.
6. 3 drops of DMACNA colour reagent were added into each standard and study specimen vial.

7. Formation of ring of bright red colour at the top of the vial indicated the presence of sulfadoxine.

Note: standard vial/tube 0 was negative control and standard vials/tubes 1, 3, and 7 were positive control.