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A CRITICAL REVIEW OF THE SOLUTIONS OF THE TREATMENT OF MALARIA- THE ILLNESS OF THE LEAST DEVELOPED WORLD

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ABSTRACT
Although the efforts have been made in the direction of the eradication of the problem of the malaria worldwide but yet there is a world of the malaria hit and malaria dense. The work critically finds the evidences of the fitness of the anti-malaria treatment in those areas of the world. It also tried to put the light on the increasing the immunity of the illness against the available treatment in the least developed world. The work is given a shape of fact finding analytical study having evidences for the justification.

Keywords: *Malaria, Treatment, Least Developed World, Illness, Treatment of Malaria*

INTRODUCTION:

Worldwide, malaria causes more than 1.5–3 million deaths each year of which more than 90% occur in under-five children in sub-Saharan Africa (Trigg and Kondrachine, 1998). The majority who suffer most are children who have not developed adequate immunity to the parasites and also in pregnant women. However, malaria is on the increase due to changes in the environment, the collapse of health systems in most developing countries south of the Sahara, and growing resistance of malaria to the most affordable anti-malarial drugs.

Despite attempts used to eradicate malaria, the disease still threatens about 40% of the world populations (300–900 million cases every year). Malaria is endemic in almost all parts of Tanzania, and it accounts for over 30–40% of the disease burden (admissions and outpatient attendances) (MoH & SW, 2006). About 70,000–100,000 under-five die annually in the country due to malaria (MoH, 2000). Malaria is a threat to every one as it affects all age groups but under-fives, pregnant women and non-immune individuals are more vulnerable than others. The cause of death in these vulnerable groups is mostly due to cerebral complications and anaemia especially in under-fives children and pregnant women. Malaria is also a major contributor to maternal deaths and low birth weights of children (WHO, 1998).

Chloroquine (CQ) has been used for many years as first line treatment drug for uncomplicated malaria in many sub-Saharan countries including Tanzania. Nevertheless, because of rapid development and spread of resistance to the drug in African countries, these countries were forced to change their anti-malarial drug treatment policies to sulfadoxine-pyrimethamine (SP). However, very unfortunately even SP lasted only for 5 years in Tanzania because resistance developed very fast in most places of the country (Schapira et al, 1993; Ronn et al, 1996). So far when Tanzania changed its anti-malarial drug treatment policy to SP in August, 2001, chloroquine resistance was more than 42% (Kitua et al, 1999), and this prevalence had surpassed WHO recommendations of changing antimalarial drug policies when resistance patterns in any country reaches 25% and above (WHO, 1994; 2002; Godfrey & Miguel, 2005). Thus, WHO classifies 4 stages or phases of resistance patterns as Grace; Alert 6-15%; Action 16-24% and Change 25% and above. These percentages or proportions relates to treatment failures rate ranges (WHO, 1994; 2002) which means individual countries should be able to take actions through their Ministries of Health or

Governments in changing antimalarial drug policies and this is what has been happening in Sub-Saharan countries where malaria is endemic and parasite resistance commonly occurs.

Tanzania is a country heavily affected by malaria, and malaria is endemic in the country. There is a widespread prevalence of the malaria mosquito with low levels of government and community resources available to combat the disease. Over 75% of Tanzania's 44 million people live in areas where malaria is highly endemic (transmission period longer than 4 months per year), and the estimated number of cases is between 14–18 million annually so people are likely to get an average of between 3-4 episodes in a year.

Thus, it is necessary to explain the scientific basis for causing skin hypersensitivity reaction leading to blisters/burns on the skin after using sulfa containing drugs like metakelfin and that these sulfa-containing drugs can cause such reported or claimed skin effects for allergic or hypersensitive individuals and that communities should know that metakelfin does not cause albinism as claimed or reported by this gentlemen from Tabora. Such claims actually are dangerous as it scares and builds trust among communities that such drugs really causes **albinism.**

This study also calls for urgent interventions to educate the public and the communities at large so that they know well that albinisms is something originating from genetical make up of an individual and does not occur in adult hood like the person who claimed to get albinism at an age of 45-47 years of age. This does not happen like this in real life as albinism occurs during early childhood/during birth of an individual.

The mass media:

In a previous study on SP it was reported by study participants about publishing side effects or severe adverse reactions caused by SP through mass media, most commonly through newspapers and radio (Nsimba, 2006). Several participants suggested that "*waandishi wa habari lazima waelimishwe namna ya kuandika habari zinazohusu madawa vizuri hasa dawa hii ya SP kwani wanavyoandika kwenye magazeti na watu wakasoma na kuona picha ya mtu aliyeunguzwa na dawa hii kila mtu anaogopa na kusema hataitumia hii dawa*" [english translation] the news media or writers should be educated about SP drug and how to write proper medical news or information in the correct way which will not scare the audience when they read. They went further to say information is very important as it may build or destroy the image of the drug. Once people have read or heard about it, it is difficult to change their mind back.

Reported healthcare workers observations and experience about SP:

Fear and and negative perceptions about SP, was previously reported by health workers regarding SP and the stated as follows "*kwa sababu ya kuona watu wanaiogopa hii dawa na akina mama wengi wakipewa wakampatie moto SP nyumbani wengine wanaitupa njiani hivyo tumeamua watoto wote wenye homa tunawapatia SP wameze hapa hapa hospitalini na tunamwangalia moto kwa muda wa nusu saa, kama hajatapika ndipo tunamruhusu mama aende na moto nyumbani na akitapika tunarudia tena kumpatia dawa*" [english translation] they had to give the drug under observation in the health facility to avoid mothers throwing away the drug (SP tablets) on their way home instead of giving them to their sick children (Nsimba, 2006).

What is albinism and the Scientific explanations on how albinism occurs or evolves/comes about:

Albinism is a genetic condition affecting the skin and sometimes it is called “achromia” or “achromatosis” or “achromasia”. This condition is characterized by a decrease in melanin production and by a partial of complete absence of pigments on the skin, hair and eyes. This hereditary disease is usually found in humans (and affects all races) including mammals, birds, fish, reptiles and amphibians (Nordqvist, 2012).

However, despite the fact albinism is a hereditary condition, in most cases, there is no history of albinism. People with albinism, often have vision problems and these people are susceptible to sunburns and skin cancers if they do not protect themselves from direct sunlight. It is reported that a person inherits one or more of the defective genes that causes them to be able to produce the normal amounts of a pigment called melanin. There are several different genes that are involved in albinism, depending on the specific type. These genes involved in albinism are located on the “autosomal chromosomes”. Autosomes are chromosomes that contain genes for general body characteristics (Nordqvist, 2012).

Genes carry genetic information that makes an individual. There are normally two copies of these chromosomes and genes; one inherited from the father and the other inherited from

the mother. Thus, albinism is a "recessive trait" meaning that a person without albinism can carry the albinism trait. Here bo th parents must carry a defective gene to have a child born who is an albino or with albinism. However, when neither parent has albinism but both carry a defective gene, there is a one to four chance that the baby will be born with albinism (Nordqvist, 2012).

Signs and Symptoms of Albinism:

Fist of all a person with albinism is generally as healthy as any other person who is not an albino. However, problems with vision and the skin are particularly common.

Vision Problems: Vision problems in albinism results from abnormal developmental of the retina and patterns of nerve connections between the eye and the brain. Thus, most people with albinism have problems with their eye sight; many have low vision. Lack of pigments in the eyes results in problems with eye sight, both related and unrelated to photosensitivity. It is this sensitivity to light which produces and leads to discomfort in bright light (Nordqvist, 2012).

Skin Problems: The dark pigment – melanin – helps to protect the skin from the sun's ultraviolet radiation. So people with albinism lacks this pigment and their skin gets burned more easily from the sun overexposure. Thus, these people need to take very special precautionary measures in order to avoid damage to the skin which is usually caused by the sun; this means they need to apply sunscreen lotions and wearing hats and sub protective clothing and eye or sun glasses (Nordqvist, 2012).

Discussion with some scientific explanations and uses of sulfa-containing drugs:

Sulfa containing drugs such as sulfadoxine-pyrimethamine (SP), trimethoprims (e.g co-trimoxazole), metakelfin and many others are or were used for treating malaria before phasing out the use of SP in 2006 in Tanzania (Nsimba, 2006; Eriksen et al, 2005), and this was due to reported increased parasite resistance against the drug. In other words the drug (SP) was no longer effective/efficacious in killing malaria parasites and in particular species of *P. falciparum* which is the most lethal specie to-date causing a lot of morbidity and mortality in Tanzania and other sub-Saharan countries (Nsimba, et al, 2002; 2005).

However, some sulfa-containing antimalarial drugs are still being used to date and in particular SP despite being phased out for treatment of uncomplicated malaria in the country in 2006. For example SP is used in the country as a prophylactic medication during pregnancy and for infants against malaria. This drug is given when pregnant women attend reproductive and child health clinics (RHC) in the country. This drug (SP) is given or administered between/during the 20^{th} -28^{th} weeks of pregnancy (IPT_1) and repeated at weeks 30^{th} to 36^{th} (IPT_2) respectively. This prophylactic measure or approach during pregnancy and for infants is termed as Intermittent Presumptive/Preventive Treatment for during pregnancy (IPTp) and Intermittent Presumptive/Preventive Treatment for Infants (IPT_i).

Apart from SP being used prophylactically, Trimethoprims like co-trimoxazole is often and widely used for treatment /management of or Pneumocystic Carinii (PCP) which is an opportunistic bacterial infection causing chest infection commonly in individuals who are HIV infected and they normally cause severe cough in these individuals. Furthermore, it is also recommended that it may be useful as a caution for both health care providers to counsel their patients so that they check and know their sero-status before being prescribed and / or using sulfa-containing drugs as there are reports that sero-positive individuals reacts or are hypersensitive to these drugs.

According to the interview conducted between the victim of metakelfin and the media/news paper and internet in early March, 2014 (http//wwmpekuzihuru.com/2014/03/mkazi-wa-tabora-asimulia-jinsi.html). The individual had the following to say in Kiswahili as we quote from what was retrieved from the news papers and internet as follows below:

The name is with held but he has 47 years by 2014 and lives in Tabora town and he gave the following information or personal history/particulars in Swahili language and here are some claims quoted in Kiswahili as he spoke with FM redio in Tanzania:

"A*medai kuwa alitumia dawa aina ya metakelfin miaka minne (4) iliyopita kwa lengo la kutibu ugonjwa wa malaria, lakini dawa hizo zilimsababishia madhara makubwa katika ngozi yake na kumpeleka kuw albino".*

Akiongea na redio Sun Rise ya 100.5 Times Fm, this individual ambaye ni mjasiriamali ameeleza kuwa alinunua dawa hizo Pharmacy na kwamba baada ya

kumsababaishia madhara hayo ameamua kujiunga na chama cha maalbino Tanzania kwa kuwa anafanana na albino wengine.

*Ameeleza kuwa katika hatua za awali za dalili mbaya ya ngozi yake, alimuona dakatari wa ngozi wa mkoa wa Tabora anaitwa Dr George. Nikaenda kumuonesha zile dalili akaniambia hii tumia tu dawa ya kwenye tubu ya hydrocortisone na baadaye itapotea hiyo, basi mimi nikatumia zile tubu za hydrocortisone, lakini ikawa hainisaidii kitu. Matokeo yake malengelenge yakahamia kwenye mguu, juu ya unyayo lakini yalikuwa hayana dalili zozote za muasho.....ameeleza (*he reported/narrated*).*

"Nikaanza utaratibu wa kupaka mafuta ya Vaseline muda kama wa wiki mbili hivi, lakini nikawa naona kama nikipaka kwenye viganja.....lakini hayaoneshi kama mafuta unayopaka kama yanaenda moja kwa moja kwenye ngozi. Ukipaka kama dakika moja hivi, ukipakaa unaona kama hujapakaa....." Hivi ndivyo mhusika alivyoiambia/isimulia Sun Rise ya 100.5 Times Fm.

Mechanism of action and kinetics of Sulfa-containing drugs:

The mechanisms of action for most of these different preparations/drugs are based on the oppression or suppression of sulfal venom synthesis digidrofolata and oppression of primetaminom transformation digidrofolieva acid tetragidrofolievu. Thus, simultaneous impact on the different stages of the germination processes (metabolism in the cell irritant, expressed synergies (finally enhancing effect) in the common application of the medicines based on the actual mechanism of inhibition.

Metakelfin is a Roman name and the drug was registered in 1998. The composition of and the form of in one tablet containing sulfametopirazine 0.5 g and 0.025 g of primetamina. Certain drugs like methotraxates and sulfa-containing drugs such as trimethoprim and pyrimethamine inhibit dihydrofolate reductase , folates (folic acid) which are essential for DNA synthesis. They are co-factors in the synthesis of purines and pyrimidines and are also necessary for reactions involved in amino acid metabolism. For activity folates must be the tetrahydro form in which it is maintained by the enzyme dihydrofolate reductase.

Dihydrofolate reductase enzyme reduces dietary folic acid to tetrahydrofolate (FH4). Folate antagonistsd act by inhibiting dihydrofolate reductase. Folates/Folic acids are used in treating megaloblastic anaemias and also in preventing or treating adverse effects from methotraxates, trimethoprims and pyrimethamines (folate anatagonists) in both humans and malaria parasites (as the prevent folate synthesis in these parasites which are essential for their survival as they do not use human made folic acid they have to make their own).

Indications for use of sulfa-containing drugs:

In addition to treatment, selective interventions like Insecticide Treated Nets (ITNs), or materials (ITMs) (WHO, 1993b; 2000), and Intermittent Presumptive Treatment (IPT) are currently applied in Tanzania and are considered as effective preventive measures (WHO, 2000; 2002; Schellenberg et al, 2001; 2003). Such ITNs, ITMs and IPT interventions are expected to improve case management as it is the primary form of prevention in Tanzania and other sub-Saharan countries. Both ITNs and IPT have been reported to reduce malaria morbidity and severe anaemia in children (Shulman et al, 1999; Schellenberg et al, 2001; 2003). A reduction in morbidity and severe anaemia means also a decrease in workload of the public health services which are already overstretched.

Most malaria diagnoses in Tanzania are based on clinical grounds. Only a few facilities are equipped with basic laboratory services which provide confirmatory diagnoses. Recently, in addition to the problem of the lack of laboratory services, where these services are available, malaria is commonly over-diagnosed. For example, the fraction of malaria-attributable fevers in health facilities in Dar es Salaam is low suggesting that patients presenting with fever are much more prone to suffer from diseases other than malaria (Wang et al, 2006). It has been reported that 87% of patients who received antimalarial treatment at the Muhimbili National Hospital in Tanzania for presumed severe malaria did not have detectable parasitaemia resulting in over-treatment of malaria and neglecting other potentially threatening conditions (Makani et al, 2003). Recently, in northeastern Tanzania it has been observed that 54% of patients treated for malaria were smear-negative for *Plasmodium falciparum* (Reyburn et al, 2004). This has important implications for the management of febrile illnesses, and over-diagnosing malaria patients may also distract from other causes of fever, some of which may be fatal (Wang et al, 2006). This may lead to a substantial number

of unnecessary treatments, drug toxicities, too costly for patients to purchase drugs and this is likely to be a problem when resistance develops to the current used expensive artemisinin-based combination therapy (ALU) in Tanzania (Mboera et al, 2006).

Chloroquine (CQ) -resistant falciparum malaria was widespread in Tanzania which led to phasing out this drug (Mutabingwa et al, 2001). This necessitated change in the National Antimalarial Drug Policy in the first-line treatment of malaria in the country in August 2001 to sulfadoxine–pyrimethamine (SP). Resistance to SP was observed in a number of places in Tanzania (Trigg et al, 1997, Lemnge et al, 1997). This prompted another change in drug policy by phasing out SP in November 2006 (Nsimba, 2006) and introducing a combination therapy (Coartem) or Artemesinin-Lumefantrine than monotherapy. Another major barrier to the successful malaria case management and preventive measures is the poor adherence to drug regimens and being non-adherent to using or sleeping under ITNs. Under-dosing is quite a common practice in many households because of poverty and the fact that clinical cure of fever is what matters to many individuals than applying the available preventive measures (Nsimba et al, 2002; WHO, 2002).

In general, sulfa-containing drugs like SP had several indications and uses as discussed above such as they were used for both treatment and prevention of uncomplicated malaria. However, they are still used as prophylactic medications used for intermittent preventive or presumptive treatment for pregnancy (IPTp) and for infants (IPTi) respectively. During pregnancy, usually the mother receives two prophylactic dose regimen at weeks between 20-24 and there after repeated between weeks 30-32 of pregnancy. These sulfadoxine-pyrimethamine (SP) tablets are administered at Reproductive Health Clinics (RHC) at booking stage.

Thus, before assigning a patient any of the sulfa-containing drugs it is a strongly advised to ask the patient if he/she has any previous nasty experience/reacted badly after taking any of these medications. However, the other most recommended approach is determining sensitivity to the hair that caused the disease in a particular patient.

So in treating malaria always appoint one dose for adults weighing 50-70 kgs (2 tablets); those weighing more than 70 kgs give 3 pills/tablets. For children give an initial dose of 25 mg/kg body weight which is approximately between the ages of 5-9 years (1/2 – 1 pill/tablet) and from the ages of 10-14 years give 1-2 tablets.

It has been reported that combined product has expressed antiprotozoal activity/actions aimed at suppressing the simplest living organisms. These sulfa containing drugs at that time before phasing them out they were quite effective against pathogens/malaria infections such as species of *P. falciparum* (the most sensitive); *P. Vivax; P. Malariae* and *P. Ovale.*

Some contra-indications of Sulfa-containing drugs:

Hypersensitivity to the drug component expressed by human liver or kidneys. Here pathological changes in the blood picture occurs. The agents are not appointed/recommended for use in children in the first two (2) weeks of life and in the last two (2) weeks of pregnancy including lactating mothers (WHO, 2002). Thus, during pregnancy and early childhood, these sulfa-containing preparations may be granted one in cases of extreme necessity and under the direct supervision of a physicians and clinical pharmacologists.

Based on these cited contra-indications for using these sulfa-containing drugs it is quite possible to relate some of these with some previous reports given for example to SP as it was believed by some communities to be too strong for children (Tarimo et al, 2001), and that the drug had characteristic properties of rapidly clearing parasites but slow fever clearance (Tarimo et al, 2000).

However, despite the above described negative perceptions and contraindications about SP and other sulfa-containing drugs like Metakelfin, these drugs were still used in most rural communities. Experience from countries like Malawi and Kenya which introduced SP as first line treatment before Tanzania, showed that people continued using chloroquine at that time after the introduction of SP as a new drug. This was due to scepticism about the efficacy of SP as a new drug and / or feared that "a potent" drug was dangerous (Bloland and Ettling, 1999).

As it can be seen after reading news papers, U-tubes about the person who was telling news writers about his terrible experience after getting laboratory results that he had malaria parasites and he went to buy from a drug shop Metakelfin about 3-5 years ago in Tabora region where he self-treated and unfortunately he got burnt the whole body and he also got hair changes which now he explains/claims by

telling the media and other people that he used this antimalarial drug-Metakelfin which has now caused or changed/turned him an albino (http//wwmpekuzihuru.com/2014/03/*mkazi-wa-tabora-asimulia-jinsi.html*; FM Radio 100.5).

So because of all these fears, negative perceptions and hesitancy of using these drugs at that time, it was connected with several factors such as; its slow pharmacological effects or actions in providing quick relief of malaria fever symptoms, instead it took up to three days or more to resolve the fever. Secondly, because of the reported rare but serious/lethal side effects which occur to some individuals being reported through mass media just like this unfortunate gentlemen who is the victim of Metakelfin from Tabora region. This is a very rare side effect which affects few individuals (1:1000) in the community/society but once it occurs it can be fatal with serious consequences/outcomes such as death. This, syndrome is medically known/called as Steven's Johnson's Syndrome. This syndrome produces adverse skin reactions leading to pealing off the skin, leaving the individual as if he/she has burns on the skin all over the body accompanied with a lot of blisters with oozing of fluids.

As there are high levels of HIV infection in some malarious areas /countries in Sub-Saharan Africa (SSA). The full effects of HIV and AIDS on the administration of antimalarial drugs are not fully clear, but some interactions exists. However, some preliminary data show that HIV infected individuals tend to have more side effects or react badly when they receive treatment with sulfa-containing drugs like sulfadoxine, metakelfin than individuals who are HIV negatives (WHO, 2002). Thus, it is quite possible in this serious scenario/event which unfortunately affected this individual (Gentleman from Tabora who is 47 years) could be a good possible explanation if he can be counseled and get confirmation of his sero-status then possible associations or linkages to his serious adverse reactions he got after swallowing metakelfin could explain reasons as to why he reacted that way.

At that time SP was seen as an expensive drug as it costed 5–11 times the price of Chloroquine (Tarimo et al, 2001. If this drug was not given for free at the public facilities, the poor Tanzanians, especially in rural communities, would not have been able to purchase the drug and this would have resulted in poor treatments and poor health seeking behaviour for malaria (Schellenberg et al, 2003; Mwenesi et al, 1995a,b; McCombie, 1996). As it was predicted for SP because of its fast development of resistance, the drug never lasted more than 5 years in Tanzania since its introduction for use after phasing out chloroquine (Nsimba, 2006; Godfrey and Miguel, 2005). Thus, in 2006 SP was phased out and a more expensive costing 6,000–10,000 Tanzania shillings (equivalent to 6–10$), but efficacious fixed combination therapy (Coartem) for uncomplicated malaria was re-introduced in 2006 in Tanzania (Nsimba, 2006; Mboera et al, 2006).

This combination therapy currently in use in the country is called artemether-lumefantrine (Coartem) but popularly known as *ALU* (short form for artemether-lumefantrine) *or dawa mseto in Kiswahili* in Tanzania. Thus, concerted efforts are required to re-educated the public/communities and also regular training for health care providers/workers to remind them on rational prescribing and use of this expensive but efficacious antimalarial drug so as reduce or delay resistance development (Nsimba, 2006; Ericksen et al, 2005).

Thus, interventions are needed and should focus more on community sensitization campaigns by using various communication approaches or strategies such as use of mass media, newspapers, radio and television about sulfa-containing drugs like metakelfin use that does not cause or lead to albinism. These communication strategies should bear correct, relevant, and short clear messages. Sensitizing and educating the people to raise their knowledge and awareness is of importance for the success of any antimalarial drug use programs/campaigns.

However, the commonest dissemination of information in the country are medias, such as newspapers and radio and on rare occasion television. Nevertheless, it is also important for educating news writers about sulfa-containing drug (s), how they work and what anticipated side effects are likely to occur after using them in order for them to write and convey proper and correct messages about these sulfa containing drugs. Wrong messages usually wins and diverts attention of majority of our people especially those living in rural communities who are the majority accounting over 75% of Tanzanians. The media diversts the attention in the wrong direction and hence believing and creating a lot of fear with a lot of negative perceptions about sulfa-containing drugs like metakelfin and many other drugs which may be useful apart from antimalarial drugs.

CONCLUSION

Communities should be educated or told that **albinisms** is not contiguous or infectious and thus, they should not fear or avoid or segregate people who are **albino** and should eat in the same pot and share most equipments without stigmatizing them. As it can be seen people with albinisms are in most cases isolated, because this condition is often misunderstood and thought to be contagious. People with albinism face social as well other cultural challenges in life. In general albinism if accompanied with a lot of social stigmatization and some of the of traditional beliefs remnants still exists in different cultures particularly in the Africa culture. Thus, this calls for societies and communities in general should make every effort not to exclude and segregate people with **albinism**.

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