ABSTRACT
Resistance of falciparum malaria to chloroquine (CQ) has gradually emerged in the late 1970s, reaching unacceptably high proportions over the following three decades of use as first line treatment in Sudan. By 2004-2006 CQ was replaced by artemisinin-based combination treatment (ACTs), with combination of sulfadoxine-pyrimethamine (SP) and artesunate (AS) deployed as first-line drug against falciparum malaria. The present review follows the evolution of CQ resistance in Sudan and the available evidence on the response to the present first-line drugs. The findings in Sudan are analyzed in view of developments in other African countries and at the global level, with the hope of elucidating possible scenarios for the course of events in the Sudan. Northern Sudan has been one of the areas where signals indicating the emergence of drug resistant malaria parasites have first originated in Africa. The pattern of low endemicity and low population immunity to malaria, together with massive deployment and improper use of anti-malarial drugs created the ideal environment for creation of anti-malarial drug resistance. Such an environment existed in certain areas in South East Asia that had historically been the epicenter from which falciparum malaria parasites resistant to pyrimethamine and chloroquine have spread to the rest of the world. The alarming recent reports about the emergence of artemisinin (ART) resistance in South East Asia have lead WHO to take specific measures for prevention, early detection and containment of drug resistance. What could be applicable in Sudan in these measures is discussed here.

Key words: Malaria, drug resistance, Sudan, chloroquine, artemisinin.

INTRODUCTION
Malaria transmission in the Northern Sudan is low-to-moderate, highly seasonal and occasionally epidemic. In the northern Sudan, in 2010, there were 2398239 reported malaria cases and 1023 deaths in the states from which information is completely available, with more than 95% of the cases being due to Plasmodium falciparum [1]. Sudan is one of the African countries in which the emergence of chloroquine (CQ) resistant falciparum malaria in Africa was first reported. An in vivo study was...
carried out in 1978, using the WHO standard in vivo test for 28 days in Gezira in Northern Sudan, and for 7 days in Bor in Southern Sudan [2]. Three cases of resistance were identified in Gezira but no cases were detected in Bor because the follow-up was done for only 7 days in the Bor area. It is possible that cases with RI resistance could have been missed. In the same year a team from WHO conducted in vitro and in vivo studies in Sennar and reported that P. falciparum had lower sensitivity to CQ by the in vitro test than other African strains, and that parasite clearance time was slower by the in vivo test than in other African cases of malaria tested [3]. A definite confirmation of the extent of CQ resistance in Sudan was first demonstrated by an in vivo study in the Khartoum area. The study was done in 1982 in 8 villages about 25 km north of Khartoum. The test was carried out in 26 patients aged 4–20 years who were observed for 28 days. Ten were sensitive, 9 had RI and 7 had RII responses. It was also noted that parasite clearance was slower and more incomplete than in the previous studies conducted in Sudan [4,5].

In the 1980s eastern Sudan faced a number of disasters, including drought, famine, floods, war and influx of refugees from Ethiopia. Under these conditions malaria outbreaks were frequent, with reports of substantial numbers of cases not responding to CQ. A study combining in vivo and in vitro assessment done in 1986 in eastern Sudan indicated 43% of P. falciparum infections investigated were resistant at RI, RII or RIII levels [6]. In another trial conducted in Gedaref State in 1987, an in vivo 28-day test for CQ efficacy was carried out on 63 patients and the response was reported as “Sensitive” (52%), “R1” (18%), “RII” (16%) and “RIII” (14%), no allowance was made for the possibility of re-infection. Blood level of CQ was measured, ruling out sub-therapeutic levels as a cause for treatment failures [7]. In a hospital-based study reported in 1992 in vivo and in vitro studies were conducted in children with falciparum malaria in central Sudan, including measurement of plasma CQ levels. Among 52 cases
tested in this study, 25% were classified as RI-RIII in the in vivo test and sub-sample of 12 isolates tested in vitro indicated that 25% of the isolates did not show a satisfactory in vitro response [8].

Therapeutic efficacy tests involving CQ and based on post-1973 WHO protocols:
Therapeutic efficacy tests (TET) for anti-malarial drugs done in Sudan since 1996- were generally based on the contemporaneous published WHO protocols for therapeutic efficacy testing [9-12] and on unpublished drafts of these protocols that appeared in-between. Consequently, these studies show some minor variations in the methodology mainly in the areas of low transmission, regarding duration of the follow-up and the inclusion criteria.

The first reported study based on post-1973 WHO protocols was done in 1997/8 [13]. Falciparum malaria cases were recruited to 5 sentinel posts in northern and central Sudan with low malaria transmission. Sampling and data analysis were done by the lot quality assurance sampling (LQAS) method [14]. Based on this method prevalence of resistant strains were proven not to be significantly less than 25% at all sentinel posts. The high level of resistance (77%) in Kassala town (Kassala State) was attributed to population movements in the Eastern borders. The test in Diling (Southern Kordofan State) also showed a high prevalence of resistance (72%) and this was suggested to be due to displacement of populations from Southern Sudan. One notable finding was that resistant cases in these low transmission areas were predominantly children, leading authors to suggest inclusion of children as a subgroup when testing efficacy in low transmission settings as they have a higher risk of therapeutic failure. At about the same time the Ministry of Health started a number of sentinel posts for monitoring therapeutic efficacy of CQ. Findings of these studies were documented in unpublished reports, [15], covering studies done during the period 1997-2002 and some of the results were presented in a regional workshop [16]. Elamin et al [ 17 ] published studies done in two rounds of testing by the Ministry of Health in 2002/2003 , testing CQ, sulfadoxine-pyrimethamine (SP) and CQ +SP in several sentinel sites in the Northern Sudan reporting an overall failure rate of CQ arm as 43.7% in the Northern Sudan and 80.2% in the Southern Sudan. In New Halfa (Kassala State) Adam et al (a) [18] conducted a randomised trial in 1999-2000 including treatment CQ, Quinine and SP. CQ efficacy rate was found to be 23.1%.

In 2001, Van der Brook et al [19] tested amodiaquine (AQ), CQ and SP efficacy in Upper Nile State of Southern Sudan. CQ and AQ produced treatment failures of 11.5% and 5.6% respectively, with no statistical difference. In another location in Western Equatoria State of Southern Sudan, Stivanello et al [20] tested AQ, CQ and SP efficacy. The results showed high failure rates to CQ (93.9%) and SP (69.9%), and a lower failure rate for AQ (25.2%).

By 2003 the published and unpublished evidence for therapeutic failure of faciparum malaria in Sudan was reviewed and CQ failure rates greater than 25% were reported in 22 out of 25 therapeutic efficacy tests conducted in different sentinel posts in Sudan [21]. In 2004, Sudan changed its malaria treatment policy, replacing CQ with artemisinin-based combination therapy, Aretesunate +SP (AS/SP) was adopted as first line treatment against falciparum malaria and aremether - lumefantrine (AL) as second-line treatment [22]. ACTs were registered in Sudan in 2006 [1].

Therapeutic efficacy tests involving SP and based on post-1973 WHO protocols:
A pyrimidine derivative, proguanil, emerged from the anti-malarial pipeline during World War II [23]. Sulfones and sulfonamides were then combined with proguanil or pyrimethamine in hopes of increasing efficacy and forestalling or preventing resistance [24]. In spite of this, by 1955 P. falciparum resistant to pyrimethamine had already been noted in Sudan [25]. Soon after Sulfadoxine/
Pyrimethamine (SP) was introduced in Thailand in 1967, resistance appeared that same year and it spread quickly throughout South-East Asia. However SP maintained its efficacy in Africa until the late 1990s but since then its resistance has spread rapidly [26]. SP was introduced in the Sudan since the early 1970s- as second line treatment for cases of uncomplicated falciparum malaria. With adoption of AS-SP combination as first line treatment against falciparum malaria in Sudan, the interest in monitoring therapeutic efficacy of SP continues. SP resistant malaria was first reported in Sudan in 1991[27].

**Table 1- In vivo studies reporting treatment failure with sulfadoxine-pyrimethamine (SP) as monotherapy and in combination with other anti-malarial drugs.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>State</th>
<th>Year</th>
<th>SP</th>
<th>SP +CQ</th>
<th>SP +AQ</th>
<th>SP +AS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adam 2004</td>
<td>New Halfa</td>
<td>Kassala</td>
<td>1999</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>18</td>
</tr>
<tr>
<td>Adam 2004a</td>
<td>New Halfa</td>
<td>Kassala</td>
<td>2001</td>
<td>16.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>28</td>
</tr>
<tr>
<td>Stivanello 2004</td>
<td>Mundri, Kajo Keji county</td>
<td>Western Equatoria</td>
<td>2001</td>
<td>69.1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>20</td>
</tr>
<tr>
<td>Van den broek 2003</td>
<td>Lankien</td>
<td>Upper Nile</td>
<td>2001</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>19</td>
</tr>
<tr>
<td>A-Elbasit 2006</td>
<td>Darawish, Kajara</td>
<td>Gedaref</td>
<td>2003</td>
<td>31.7</td>
<td>36.6</td>
<td>ND</td>
<td>ND</td>
<td>29</td>
</tr>
<tr>
<td>Salah 2005</td>
<td>Kassala Town</td>
<td>Kassala</td>
<td>2003</td>
<td>15</td>
<td>2.5</td>
<td>ND</td>
<td>ND</td>
<td>30</td>
</tr>
<tr>
<td>Elamin 2007</td>
<td>Obeid</td>
<td>Gezira</td>
<td>2003</td>
<td>4.2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>17</td>
</tr>
<tr>
<td>Elamin 2007</td>
<td>Medani</td>
<td>Kassala (Kassala state)</td>
<td>2003</td>
<td>7.7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>17</td>
</tr>
<tr>
<td>Elamin 2007</td>
<td>Khartoum</td>
<td>Khartoum</td>
<td>2003</td>
<td>ND</td>
<td>14.5</td>
<td>ND</td>
<td>ND</td>
<td>17</td>
</tr>
<tr>
<td>Elamin 2007</td>
<td>Damazin</td>
<td>Blue Nile</td>
<td>2003</td>
<td>4</td>
<td>5.9</td>
<td>ND</td>
<td>ND</td>
<td>17</td>
</tr>
<tr>
<td>Hamour 2005</td>
<td>Limun village</td>
<td>Southern Kordofan</td>
<td>2003</td>
<td>ND</td>
<td>ND</td>
<td>7.2</td>
<td>8.8</td>
<td>33</td>
</tr>
<tr>
<td>Adam 2005</td>
<td>Kassala</td>
<td>Kassala</td>
<td>2004</td>
<td>13.3</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>Mohamed 2006</td>
<td>Kosti</td>
<td>White Nile</td>
<td>2004</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Elamin 2005</td>
<td>Damazin</td>
<td>Blue Nile</td>
<td>2004</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Elamin 2005</td>
<td>Kassala Town</td>
<td>Kassala</td>
<td>2004</td>
<td>ND</td>
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<td>ND</td>
<td>4</td>
<td>37</td>
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<tr>
<td>Elamin 2005</td>
<td>Kosti</td>
<td>White Nile</td>
<td>2004</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Elamin 2005</td>
<td>Malakal</td>
<td>Upper Nile</td>
<td>2004</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Van Den Brock 2005</td>
<td>Malakal</td>
<td>Upper Nile</td>
<td>2003-4</td>
<td>ND</td>
<td>ND</td>
<td>1</td>
<td>0.9</td>
<td>39</td>
</tr>
<tr>
<td>Ibrahim 2007</td>
<td>New Halfa</td>
<td>Kassala</td>
<td>2005</td>
<td>ND</td>
<td>4.8</td>
<td>2.5</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Mukthar 2007</td>
<td>Asar, Abunaja Juama, Abunaja Bargo</td>
<td>Gedaref</td>
<td>2004-5</td>
<td>ND</td>
<td>ND</td>
<td>15.6 (6.5)</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

AQ - amodiaquine, AS - artemesunate, CQ - chloroquine, ND - not done, SP - sulfadoxine-pyrimethamine.
TETs evaluating SP as monotherapy or in combination with other anti-malarials. With the exception of two studies that reported no treatment failures with SP monotherapy in surveys conducted in 1999 in Kassala [18] and in 2001 in Upper Nile (Southern Sudan) [19], other studies reported variable rates of treatment failures with SP monotherapy [17, 20, 28, 29, 30, 31]. SP in combination with CQ was then tested in Gedaref in Eastern Sudan where this combination resulted in high treatment failure rates comparable to SP alone [29]. Combination of AQ+ SP resulted in low failure rates of 1% in Malakal (Upper Nile State), [39], and 4.8% New Halfa (Kassala State), [32] and 7.2% in Nuba Mountains in Southern Kordofan State [33, 34]. In conclusion, TETs on SP have provided evidence of emerging treatment failure with SP in Sudan. The emergence of SP resistance in Easter Sudan is confirmed by longitudinal observations with resistance markers which show a dramatic increase in the frequency of Pf dhfr 108N allele between 1998 and 2000 which is believed to reflect drug pressure due to increased SP usage during this period [35].

Five reported therapeutic efficacy tests conducted in 2003 -2004 for combination of SP +AS showed 100% efficacy of this combination against falciparum malaria in some sites in Northern and Southern Sudan whereas other sites show treatment failure rates ranging from 2 to 15.6 % in Northern and Southern Sudan. It is possible that efficacy of this combination is starting to be compromised by a growing resistance to the SP component as evidenced by 31.7 % failure rate of SP in Darawish in eastern Sudan [29].

Therapeutic efficacy tests involving other ACTs based on post 1973 WHO protocols:
Salah et al in 2005 [40], evaluated Artemether-Lumefantrine (AL) suspension amongst 48 children in Kassala in Eastern Sudan. All patients showed no clinical or parasitological failure by day 3. In Gedaref State, Mukthar et al 2007 [38] conducted TET study in 3 villages for SP +AS and AL efficacy was 93.5% and 91.3% for SP +AS and AL respectively.

In 2003, the efficacies of mefloquine monotherapy and of an artesunate–mefloquine (AS+MQ) combination, against falciparum malaria, were investigated and compared in New Halfa, in eastern Sudan [41]. MQ was given at a dose of 25 mg/kg, AS+MQ at 4 mg/kg/day for 3 days followed by single-dose of MQ at 15 mg/kg. The cure rates were 92.5% after MQ and 94.7% after the AS+MQ combination. Although the treatments appeared equally effective in clearing parasitaemias, the combination was better at clearing gametocytaemias and was less likely to cause adverse side-effects. It is unclear why MQ given alone was almost 10-fold more likely to trigger adverse effects than treatment with a combination that contained the same drug. The authors suggest that this could be a reflection of the different mefloquine doses.

In 2010 Elamin et al [42] tested AL efficacy in 4 sentinel sites in Damazin (Blue Nile State), Sennar (Sennar State), Kosti (White Nile State) and Juba (Bah el-Jabal State). Although ETF and LCF were not excluded from the denominator in calculation of the proportion of treatment failures but figure for treatment failures still remained less than 5%.

Currently, TET in Northern Sudan is based in four sites in Kassala, Gezira, Blue Nile and White Nile States. Tests for artemisinin + piperaquine granules and tablets conducted in 2008 resulted in adequate clinical and parasitological response of 96.2% and 100 % respectively [43,44].

Studies on molecular markers of anti-malarial drug resistance in Sudan:
Studies on molecular markers in Sudan have mainly aimed at estimating the prevalence of the molecular markers of SP and CQ resistance and validation of the association of these markers with resistance in different locations for policy guidance as well for better understanding the evolution and epidemiology of drug resistance.
CQ resistance markers:
Studies on CQ resistance markers Pf CRT and Pf mdr1 have covered different parts of Northern Sudan and Southern Sudan [45-53, 55-65]. Cross-sectional studies have indicated geographic variations in the prevalence of these genes between sites in Eastern Sudan and central Sudan and the significant geographic differences have been attributed to differences in drug pressure [59]. Moreover, longitudinal studies in one locality in eastern Sudan, where there are short and seasonal malaria epidemics, over the course of a 12-year period, indicated a steady increase in frequencies of the mutant alleles of pfcrt and pfmdr1 [35]. In addition, these studies revealed that these genes fluctuated significantly between the wet and the dry seasons, probably due to drug pressure. In spite of the fact that CQ has been abandoned as first line treatment for falciparum malaria, recent surveys show that the CQ resistance markers are still highly prevalent in endemic areas in Central and Eastern Sudan [56].

The correlation between drug resistance markers and treatment failure has recently been studied at the global level in a meta-analysis of published studies [54]. This analysis concluded that the risk of therapeutic failure after CQ was increased by the presence of Pfcrt K76T and that Pfmdr1 N86Y was associated with both CQ and AQ failures. In Sudan, reports on the association of CQ resistance markers with response to treatment with anti-malarials show some discrepancies. Menegon et al [56] tested the correlation between in vitro susceptibility to CQ and the presence of single and double mutations Pfcrt T 76 / Pfmdr1 Y 86 of CQ in a sample of 45 isolates from Central and Eastern Sudan. They reported a low correlation between molecular profile of both genes and their in vitro susceptibility. This has not been fully explained but could be attributed to the small number in the test sample of that particular study. In fact, Sudanese isolates of P. falciparum lacking Pfmdr1 were first reported in 1991 [60]. The chemotherapeutic model also shows variable results. In an area of stable transmission in the Southern Sudan a strong association between CQ resistance markers and treatment failure was reported [57]. However, studies in areas of low transmission in Sudan found variable patterns of association between CQ treatment failure and polymorphisms pfcrt K76T and pfmdr1N86Y. Some studies found no association of these markers with clinical outcome [48, 53]. Gadalla [50] found a strong association of these markers with early treatment failure but not with the overall treatment response with CQ. Babiker et al [45] found significant association of treatment failure with pfcrt T76 polymorphism but association with pfmdr1 Y86 only in clones with pfcrt-T76, suggesting that pfmdr1 –Y86 augments drug resistance but only when pfcrt-76 is found in the same genome. Khalil et al [47] compared the association of CQ markers with response to treatment in Sudan and Tanzania. They found significant association between resistance markers and treatment failure in Sudanese isolates but not in isolates from Tanzania. They suggest that most of these discrepancies in the in vivo therapeutic model are probably related to host factors such as immunity and the parasite biomass at the start of treatment.

SP resistance markers:
Although SP is no longer recommended as monotherapy against falciparum malaria, it is still being used in combination with artesunate as first line treatment in Sudan as well as in other countries in the region. It follows that efficacy of the SP component should be closely monitored to ensure the effectiveness of the combination therapies that include it. The prevalence of point mutations Pf dhfr and Pf dhps have been reported from different parts of Sudan. A notable feature is that the latter surveys show high frequencies of mutations S108N and N51I either as individual mutations or as a combined double mutation in areas of low transmission in central and eastern Sudan.
This allele of *P. falciparum* parasites in eastern Sudan has been associated with in vitro resistance to pyrimethamine [46, 67], and has shown an increase in prevalence in the eastern Sudan corresponding to increased SP failure. Surveys conducted in Sudan also indicate low frequency of mutant IRN-GE haplotype which is commonly indicated as a good predictor of treatment failure [68]. Also, mutation Pfdhfr C59R which is also a good predictor of treatment failure [80,81], is absent or is very rare is Sudan. However, the frequency of this mutation in Sudanese isolates has significantly increased from 0.6% in 2002-3 to 8.8% in 2007 in areas of low transmission suggesting emergence of SP resistance [56]. Al-Saai et al [65] described resistant haplotypes of Pfdhfr and Pfdhps in Asar in eastern Sudan distinct compared to common haplotypes thought to be the sources of resistance to SP in other African countries[73-79]. They conducted microsatellite studies of these haplotypes and the local genotypes suggested that resistant haplotypes in this area may have evolved locally.

The relationship between SP molecular markers and parasite clearance after treatment is rather complex. This relationship has been studied by A- Elbasit et al [49] who concluded that there are at least three factors directly contributing to parasite clearance: the drug (SP), immunity (represented by age) and parasite mutations (more than one mutation). They suggested that, the dhfr/dhps mutations provide the parasite the ability to resist chemotherapy, while it renders it more susceptible to the host immunity.

Molecular marker screening should be carried out in the frame of country surveillance activities. Monitoring evolution of *P. falciparum* drug resistance by analyzing the prevalence of drug resistance mutations in an endemic area as Sudan, where both logistical and political problems make the implementation of the therapeutic efficacy tests difficult, could provide key information for the deployment of an effective national malaria treatment drug policy.

5: The threat of emergence of artemisinin resistance:

Recently, partial artemisinin-resistant falciparum malaria has emerged on the Cambodia–Thailand border [82, 83, 84]. The first signals came from the Thai Cambodian border when the authorities noted that routine surveillance data indicated a progressive failure of ACTs against falciparum malaria. Comprehensive studies with artemesunate combined with mefloquine and as monotherapy have confirmed significant delay of parasitemia clearance in this area. In some cases there was evidence resistance manifesting as treatment failure. Several factors may have contributed to the emergence of reduced artemisinin sensitivity in Cambodia which was one of the first countries to adopt ACTs as a first-line treatment in 2001, but unregulated artemisinin combination or as a monotherapy has been available since the mid-1970s. Counterfeited or substandard tablets that contain less active ingredients than stated are additional sources of subtherapeutic dosing of artemisinins, which may also have contributed to the selection of resistant parasite strains. It is possible that the different pharmacokinetic properties of artemisinins in subgroups of the population, such as pregnant women and children, have resulted in under-dosing. Why has this problem emerged in western Cambodia and not in other parts of the world? Several factors have probably played a role:

1. The artemisinins have been used for a long time (30 years) in this area, whereas most other countries have a shorter experience with these drugs.
2. There has been unique massive drug pressure.
3. The low malaria transmission in the area was probably essential to allow resistant parasite populations to establish themselves.
4. It is also possible that parasite factors, such as a unique *P. falciparum* phenotype or host factors have played a part. Western Cambodia has previously been a focal point for the emergence
of chloroquine resistance and for sulfadoxin–pyrimethamine resistance. At some time resistance to the artemisinins was not considered to be a significant threat based on what was widely circulated about its use for centuries in China, without emergence of resistance. Now we know the fact that resistance to the artemisinins does happen. Yet, it is important to stress that the emerging resistance to artemisinins is still limited and will remain geographically limited for some time. However, judging from the history of anti-malarial drugs, this resistance is bound to reach Africa. That would be a real challenge since we still have no replacement for the artemisinins. A multifaceted containment programme has recently been launched by WHO in a programme called Global Plan for Artemisinin Resistance Containment (GPARC) [85]. The plan aims at prevention, early detection and containment of resistance to the artemisinins, with the goal of containment or elimination of artemisinin resistance where it already exists and prevents artemisinin resistance where it has not yet appeared. It is apparent that the Sudan harbours the environment for creation of drug resistant malaria parasites as evidenced by the early and rapid spread of resistance to CQ. Besides the massive use of anti-malarials, there is a pattern of low endemicity which has been associated with spread of drug resistant malaria as shown by mathematical models [86]. The current threat of resistance to artemisinin should call for promotion of early diagnosis and appropriate treatment, decreasing drug pressure, optimising vector control, targeting the mobile population, strengthening management and surveillance systems, and operational research. Therapeutic efficacy trials recently conducted in Sudan have provided valuable evidence to guide the country’ national treatment policy. An even closer monitoring of the response to the present first line treatment ( sulfadoxine-pyrimethamine plus artesunate) is needed. Of particular concern are the results of monitoring studies indicating treatment failure of first line treatment ACTs in eastern Sudan [38]. There is also evidence of increasing prevalence of markers suggesting resistance to the antifolates in the Sudan [56]. This raises concern since failure of SP as a partners drug in artemisinin-based combination would lead to failure of treatment with ACT and exposes artesunate to drug pressure leading to emergence of resistance to the artemisinins. In terms of practical steps to be taken we need to do the following:

1. Monitoring response to anti-malarials:
   We need to conduct regular rounds of monitor drug efficacy using the standard in vivo efficacy study protocol with ACT. If >10% positive after 72 hours, this could be an indication that we need further studies. It is important to note that treatment failure with ACT does not necessarily mean artemisinin resistance. To confirm the possibility of ART resistance we need to conduct a special study with ART monotherapy for 7 days, with the following additional monitoring parameters:
   1. Parasite positivity at day 3 after treatment
   2. Pharmacokinetic measurements
   3. Parasite clearance time
   4. PRR (Parasite reduction ratio) in 48 hours
   5. Slope of the linear parasite clearance curve

2. Taking measures to prevent or delay emergence of resistance:
   This could be achieved by making effective ACTs of good quality widely accessible and correctly used, particularly in the private sector, which includes:
   1. Education of the practitioners
   2. Increase compliance by users of ACTs
   3. Better diagnosis of the disease to avoid misuse of the medicines
   4. Transmission control to reduce the burden and the use of anti-malarial drugs (less drug pressure) vector control and bed-nets
5. Reduction of reservoir of infection (responsible for the spread of drug resistance) in improving therapeutic practice, in particular early diagnosis, effective treatment, and use of gametocytocidal drugs

At one time resistance to the artemisinins was not considered to be a significant threat based on what was widely circulated about how it has maintained potency against malaria parasites for centuries in China. Now we know the fact that resistance to the artemisinins does happen although it has so far been confirmed in a small number of individual cases in a limited geographic area. There is no evidence now that ART resistance has spread to Africa but, judging from the history of anti-malarial drugs, this resistance is bound to reach Africa. It is just a matter of time.

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