http:// ijp.mums.ac.ir

Review Article (Pages: 7901-7928)

Clinical Pharmacology of the Antimalarial Artemisinin-Based Combination and other Artemisinins in Children

*Gian Maria Pacifici[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

In 2010, there were estimated 219 million cases of malaria resulting in 666,000 deaths and two-thirds were children. Children are more vulnerable than adults to malaria parasites. In sub-Saharan African countries, maternal malaria is associated with up to 200,000 estimated infant deaths yearly. Malaria is caused by five Plasmodium parasites namely: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi. Of these, Plasmodium falciparum accounts for the majority of the burden of malaria infection in sub-Sahara African countries and is associated with most severe disease. Plasmodium vivax accounts for half of the malarial burden infection in South and East Asia and > 80% of the malarial infections in the America. The artemisinins are very potent and fast-acting antimalarials, inducing more rapid parasite clearance and fever resolution than any other currently used of antimalarial drugs. They are particularly well suited for the treatment of severe Plasmodium falciparum malaria.

The standard treatment of malaria infection employs artemisinin-based combination therapy. This antimalarial drug increases treatment efficacy and reduces selection pressure for the emergence of drug resistance. Artemisinins cause a significant reduction of the parasite burden, with a reduction in the parasite population. Only three to four cycles (6 to 8 days) of treatment are required to remove all parasites from the blood. Artemisinins are formulated for oral, intramuscular, intravenous, and rectal routs. Bioavailability after oral dosing is ≤ 30%. The aim of this study is to review the published data on the clinical pharmacology of artemisinins in children.

Key Words: Antimalarial drugs, Artemisinins, Children, Effects, Resistance, Safety.

*Please cite this article as: Pacifici G.M. Clinical Pharmacology of the Antimalarial Artemisinin-Based Combination and other Artemisinins in Children. Int J Pediatr 2018; 6(7): 7901-28. DOI:

Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacifici@biomed.unipi.it

Received date: Mar.22, 2018; Accepted date: Apr.22, 2018

1-INTRODUCTION

In 2010, there were estimated 219 million cases of malaria resulting in 666,000 deaths and two-thirds were children. Children are more vulnerable than adults to malaria parasites. In sub-Saharan African countries, maternal malaria is associated with up to 200,000 estimated infant deaths yearly. Five Plasmodium species are known to infect humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi. Plasmodium falciparum and Plasmodium vivax cause most of the malarial infections worldwide. Of these, Plasmodium falciparum accounts for the majority of the burden of malaria infection in sub-Sahara Africa and is associated with most severe disease. Plasmodium vivax accounts for half of the malarial burden infection in South and East Asia and > 80% of the malarial infections in the America, Vinetz et al. (1).

Malaria in humans is caused by intraerythrocytic protozoa of the genus Plasmodium. These parasites are transmitted by the bit of an infective female Anopheles mosquito. Malaria surveillance in the United States is conducted to identify episodes of local transmission and to guide prevention Polymerase chain reaction (PCR) recommendations for travelers in malaria endemic countries. Malaria cases diagnosed by blood film or rapid diagnostic test of Centers for Disease Control and Prevention are mandatory to be reported to local and state health departments by health care providers or laboratory staff. Case investigations are conducted by local and state health departments, and reports are transmitted to Centers for Disease Control and Prevention through the National Malaria Surveillance System, National Notifiable Diseases Surveillance System, or direct Centers for Disease Control and Prevention consultations. Centers for Disease Control and Prevention conducted antimalarial drug resistance marker testing on blood samples submitted to the Centers for Disease Control and Prevention by health care providers or local/state health departments (2). Artemisinin are very potent and fast-acting antimalarial, inducing more rapid parasite clearance and fever resolution than any other currently used antimalarial drugs. They are particularly well suited for the treatment of severe Plasmodium falciparum malaria and are also affected against the asexual erythrocytic stages of Plasmodium vivax. The standard treatment of malaria employs artemisinin-based combination therapies to increase treatment efficacy and reduce selection pressure for the emergence of drug resistance. Artemisinins cause a significant reduction of the parasite replication and egress (1). Only three to four cycles (6 to 8 days) of treatment are required to remove all the parasites from the blood (3). Additionally, artemisinins possess some gametocytocidal activity which leading to a decrease in malaria parasite transmission. Artemisinin-based combination therapy has low toxicity and is considered safe for use in non-pregnant adults and children.

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE via (PubMed), EMBASE, Google scholar as search engines; February 2018 was the cutoff point. Key references from extracted papers were also hand-searched.

2-2. Search Terms

The following key words "artemisinin neonates", "artemisinin effects neonates", "artemisinin pharmacokinetics neonates", "artemisinin metabolism neonates" and "artemisinin resistance neonates", were used.

3-RESULTS

3-1. Mechanisms of Action of Artemisinins

Most studies concur that the activity of artemisinins results from reductive scission of the peroxide bridge by reduces heme iron. In addition, to the formation of potentially toxic heme-adducts, activated artemisinins might in turn generate free radicals that alkylate and oxidize proteins and possibly lipids in parasitized erythrocytes (4).

3-2. Administration routes of Artemisinins

The semisynthetic artemisinins may be administrate orally (dihydroartemisinin, artesunate, and artemether), intramuscularly (artesunate and artemether), intravenously (artesunate), and rectally (artesunate). Bioavailability after oral dosing typically is $\leq$ 30%. Although artemisinins rapidly achieve the peak serum level; intramuscular administration of the lipid-soluble artemether packs in 2-6 hours, due to a depot effect at the injection site (1). Rectal administration of artesunate has emerged as an important administration route, especially in tropical countries where it can be lifesaving. However, drug bioavailability via rectal administration is highly variable among individual patients (5).

3-3. Safety of artemisinin-based combination and other artemisinins in children

A Pilot Programme of Cohort Event Monitoring was conducted across the six geopolitical zones of Nigeria on patients treated for uncomplicated malaria infection with artemisinin-based combination therapy. The emergence and spread of malarial parasites resistance to commonly available antimalarial drugs necessitated a shift in policy for malaria treatment by the Federal Government from the use of chloroquine and sulfadoxine/pyrimethamine as first-line treatment to artemisinin-based combination. Initial reports following development of artemisinin-based combination treatment in clinical settings raised safety concerns regarding their use. Although artemisinin and derivatives are generally thought to be save, there are currently few or no data on their safety among population of Nigeria (6). The seven most common adverse advents were general weakness N =25.0 (36.6%); dizziness N = 11.9 (17.2%); vomiting N = 8.0 (10.2%); abdominal pain N = 8.5 (7.2%); insomnia N = 6.3 (5.9%); body pains N = 3.4 (5.2%); and anorexia N = 8.5 (4.6%). Most adverse events occurred from day 1 and peaked by days 2 and 3 of medication with the mean duration of events being 3 days. By the end of the following-up visit on day 7, the adverse events had resolved in the majority of patients. Adverse events were more common in the artesunate-amodiaquine group than artemether-lumefantrine revealing a better safety profile for artemether-lumefantrine ($p < 0.001$).

Artemisinin-based combination therapy demonstrated good ability to resolve the clinical symptoms of uncomplicated malaria infection. In conclusion, this pilot Cohort Event Monitoring programme suggests that adverse events with artemisinin-based combination therapies were uncommon and serious life-threatening events were not common. It appears that artemisinin-based combination therapies have a tolerable safety profile among Nigerians. An increasing number of countries in sub-Saharan Africa are changing to artemisinins combination therapy as first or second line treatment for malarial infection. There is an urgent need to assess the safety of these drugs in pregnant women who may be inadvertently exposed

to or actively treated with artemisinin-based combination therapies (7). Fourteen relevant studies (nine descriptive case reports and five controlled trials) were identified. Numbers of participants in these studies ranged from 6 to 461. Overall there were reports on 945 women exposes to an artemisinin-based combination during pregnancy, 123 in the first trimester and 822 in the second or third trimesters. The primary endpoints for these studies were drug efficacy and parasite clearance. Secondary endpoints were birth weight, pre-term birth, pregnancy loss, congenital anomalies and developmental milestone.

While none of the studies found evidence for an association between the use of artemisinin compounds and increased risk of event rates that could be of public health importance. Heterogeneity between studies in the artemisinin and comparator drugs, and in definition of adverse pregnancy outcomes, limited any pooled analysis. The limited data available suggest that artemisinins are effectively and unlikely to be cause of fetal loss of abnormalities, when used in late pregnancy. However, none of these studies had adequate power to rule out rare serious adverse events, when in the 2nd and 3rd trimesters and there is not enough evidence to effectively assess the risk-benefit profile of artemisinin compounds for pregnant women particularly for the 1st trimester exposure. Methodologically rigorous, larger studies and post-marketing pharmacovigilance are urgently required.

Egunsola and Oshikoya (8) compared the safety of artemether-lumefantrine with artemisinin-based combination in children. Four thousand, seven hundred and twenty six adverse events were recorded in 6,000 patients receiving artemether-lumefantrine. Common adverse events (≥ 1/100 and < 1/10) included: coryza, vomiting, anemia, diarrhea, vomiting and abdominal pain; while cough was the only very common reported adverse events (≥ 1/10). Artemether-lumefantrine-treated children have a higher risk of body weakness (64%) than those on artesunate-mefloquine (58%) (Relative risk = 1.12; 95% confidence interval = 1.04-1.21; p = 0.004). The risk of vomiting was significantly lower in patients on artemether (88%) than artesunate-amodiaquine (10.6%) (Relative risk = 0.76; 95% confidence interval = 0.63-0.90; p = 0.002). Similarly, children on artemether-lumefantrine had a lower risk of vomiting (1.2%) than Chlorproguanil/dapsone/artesunate treated children (5.2%) (Relative risk = 0.63; 95% confidence interval = 0.47-0.58; p = 0.002). The risk of serious adverse events was significantly lower for artemether-lumefantrine (1.3%) than chlorproguanil-dapsone-artesunate (5.2%) (Relative risk = 0.45; 95% confidence interval = 0.27-0.74; p = 0.002).

3-4. Efficacy of artemisinin-based combination and other artemisinins in children

The use of drug combinations, including non-artemisinin-based and artemisinin-based combination therapy, is a novel strategy that enhances therapeutic efficacy and delays the emergence of multiple-resistant Plasmodium falciparum (9). Its use is strongly recommended in most sub-Saharan African countries, namely Cameroon, where resistant to chloroquine is widespread and antifolate resistance is emerging. Studies were conducted in children with acute uncomplicated Plasmodium falciparum malarial infection according to the standard World Health Organization (WHO) protocol at four sentinel sites between 2003 and 2007. A total of 1,401 children were enrolled, of whom 1,337 were assigned to randomized studies and 64 were included in a single non-randomized study. The proportions of

adequate clinical and parasitological response (PCR-uncorrected on day 14 and PCR-corrected on day 28) were the primary endpoints to evaluate treatment efficacy on day 14 and day 28. The relative effectiveness of drug combinations was compared by a multi-treatment Bayesian random-effect meta-analysis. The results based on the meta-analysis suggested that artesunate-amodiaquine is as effective as other drugs (Artesunate and sulfadoxine-pyrimethamine, Artesunate+chlorproguanil-dapsone, artesunate–mefloquine, dihydroartemisinin–piperaquine, artemether-lumefantrine, amodiaquine, and sulfadoxine-pyrimethamine and amodiaquine).

Although artemether-lumefantrine requires six doses, rather than three doses for other artemisinin-based combinations, it has potential advantages over other forms of artemisinin-based combination therapy. Further studies are needed to evaluate the clinical efficacy and tolerance of these combinations in different epidemiological context. Artesunate plus sulfadoxine-pyrimethamine and artemether plus lumefantrine are the first- and second line treatments, respectively, for the treatment of Plasmodium falciparum infections and dihydroartemisinin plus piperaquine is a potential candidate in case artesunate plus sulfadoxine-pyrimethamine or artemether plus lumefantrine fails in Pakistan (10). The therapeutic efficiencies (5 sites in 2007, 2 sites in 2011 and 2 sites in 2012), artemether (2 sites in 2012), and dihydroartemisinin plus piperaquine (2 sites in 2015) were evaluated in seven sentinel sites. Clinical and parasitological outcomes were evaluated among eligible patients. Mutations of the Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase were genes investigated. After PCR correction, a 98.5 to 100% adequate clinical and parasitological response for artesunate, plus sulfadoxine-pyrimethamine, and 98.8 to 100% adequate clinical, and parasitological for artemether plus lumefantrine was observed by day 28, as well as a 100% adequate clinical and parasitological response by day 42 for dihydroartemisinin plus piperaquine. The prevalence of mutants of dihydrofolate reductase and dihydropteroate synthase genes was investigated. The prevalence of mutants of dihydrofolate reductase (C59R/S108N), and dihydropteroate synthase mutant was dominant (96.6% to 100%) at all sites. Artesunate plus pyrimethamine remains highly effective in Pakistan. However, molecular data indicate that sulfadoxine-pyrimethamine resistance is being established, although mutations that confer a high risk of sulfadoxine-pyrimethamine treatment failure are rare or non-existent. This underscores the need for close monitoring of both in-vivo artesunate plus sulfadoxine-pyrimethamine efficacy and dihydrofolate reductase and dihydropteroate synthase mutations to inform national treatment policy.

3-5. Recommendation to administrate artemisinin-based combination over other anti-malarial drugs in children

New malaria infection guidelines in Tanzania have led to the large-scale development of artemether-lumefantrine (Coartem), popularly known as Artemether/Lumefantrine (ALu) or dawa mseto. Very little is known about how people in malaria endemic areas interpret policy markers' decision to replace existing antimalarials, such as sulphadoxine-pyrimethamine with "new" treatment regimens, such as ALu or other formulations of artemisinin-based combination therapy [Kamat and Nyato 2010]. While more than two-thirds of the mothers had an overall negative disposition toward sulphadoxine-pyrimethamine, 97.5% of them spoke favorably about ALu, emphasizing its

ability to help their children to rapidly recover from malaria infection, without undesirable side-effects. A percentage of 62.5 of the mothers reported that they were spending less money dealing with malaria infection than previously when their children were treated with sulphadoxine-pyrimethamine. A percentage of 88 of the mothers had waited for 48 hours or more after the onset of fever before taking their children to the dispensary.

Mothers' knowledge and reporting of ALu's dosage was, in many cases, inconsistent with the recommended dosages schedule for children. Development of ALu has significantly changed community level perceptions of anti-malarial treatment. However, mothers continue to delay seeking care before accessing ALu, limiting the impact of highly subsidized rollout of the drug. Implementation of artemisinin-based combination treatment guidelines must be complemented with educational campaigns to insure that mothers seek prompt help for their children within 24 hours of the onset of fever. Improved communication between health care providers and mothers of sick children can facilitate better adherence to ALu's recommended dosage. Community level interpretations of anti-malarials are multifaceted: integrating knowledge of local beliefs and practices surrounding consumption of anti-malarials into programmatic goals can help to significantly improve malaria infection control interventions. Following the development of resistance to anti-malaria mono-therapies, malaria endemic countries in Africa now use artemisinin-based combination therapy as recommended the first-line treatment for uncomplicated malaria infection. Patients' adherence to artemisinin-based combination therapy is an important factor to ensure treatment efficacy, as well as to reduce the likelihood of parasite resistance to these drugs. Lawford et al. (12) report adherence to a specific artemisinin-based combination therapy, under conditions of routine clinical practice in Kenya. Of the 918 patients included in the study, 588 (64.1%) were "probably adherent", 291 (31.7%) were "definitely non-adherent" and 39 (4.2%) were "probably non-adherent". Six factors were found to be significant predictors of adherence: patient knowledge of the artemisinin-based combination therapy dosing regimen (odds ratio = 1.76; 95% confidence interval = 1.32-2.35), patient age (odds ratio = 1.65; 95% confidence interval = 1.02-1.85), respondent age (odds ratio = 1.37; 95% confidence interval = 1.10-2.48), whether a respondent had seen artemether-lumefantrine before (odds ratio = 1.46; 95% confidence interval = 1.08-1.98), whether a patient had reported dislikes to artemether-lumefantrine (odds ratio = 0.62; 95% confidence interval = 0.47-0.82), and whether a respondent had waited more than 24 hours to seek treatment (odds ratio = 0.73; 95% confidence interval = 0.054-0.99).

Overall, adherence to artemether-lumefantrine was found to be low in both Garissa and Bunyala districts, with patient knowledge of the artemether-lumefantrine dosing regimen found to be strongest predictor of adherence. Interventions aimed at increasing community awareness of the artemether-lumefantrine dosing regimen, use of child friendly formulations and improving health workers' prescribing practices are likely to ensure higher adherence to artemether-lumefantrine and eventual treatment success. Malaria-endemic countries are switching antimalarial drug policy to artemisinin-based combination therapies and the global community is considering the setting up of a global subsidy mechanism in order to make them accessible and affordable. However, specific interventions may be needed to reach remote at-risk communities and to ensure that they are

used appropriately (13). This analysis documents the coverage with artemisinin-based combination therapies versus artemisinin monotherapies, and the effectiveness of malaria outreach teams and Village Malaria Workers in increasing access to appropriate diagnosis and treatment with artemisinin-based combination therapies in Cambodia, the first country to switch national antimalarial drug policy to an artemisinin-based combination therapy of artesunate and mefloquine in 2000. In areas without specific interventions, only 17% (42/251) of respondents received a biological diagnosis, 8% (17/206) of respondents who received modern drug did so from a public health facility, and only 8% of them (17/210) received artesunate and mefloquine; worryingly, 78% (102/131) of all artemisinins use in these areas as a monotherapy. However, both the Village Malaria Worker scheme and malaria outreach team scheme significantly increased the likelihood of being seen by a trained provider (adjusted odds ratios of 148 and 4, respectively), and of receiving artesunate and mefloquine (adjusted odds ratios of 2.7 and 7.7, respectively).

The coverage rates of appropriate diagnosis and treatment of malaria were disappointingly low and the use of artemisinin monotherapy alarmingly high. This reflects the fragmented nature of Cambodia's health system in remote areas and the reliance placed by these communities on informal vendors from whom artemisinin monotherapies are widely available. However, Village Malaria Workers in particular are an effective means of improving access to malaria diagnosis scheme and the social marketing of rapid diagnostic tests and blister-packaged artesunate and mefloquine have both been scaled up nationally. Case management in the public sector has also reportedly improved. Given recent concerns regarding the development of artemisinin drug resistance in the Thai-Cambodia border, the effectiveness of these measures in reducing the use of artemisinin monotherapy needs to be urgently re-evaluated. Artemisinin-based combination therapies are the most effective treatment for uncomplicated Plasmodium falciparum malaria infection. A commonly used indicator for monitoring and assessing progress in coverage of malarial infection treatment is the proportion of children younger than 5 years with reported fever in the previous 14 days who have received artemisinin-based combination therapy. Bennett et al. (14) obtained data on 201,704 children younger than 5 years from 103 surveys across 33 countries.

A rapid diagnostic test results were available for 40 of these surveys including 40,261 (20%) children, and these authors predicted a rapid diagnostic test status for the remaining 161,443 (100%) children. The present findings showed that artemisinin-based combination therapy coverage in children younger than 5 years with a fever and Plasmodium falciparum infection increased across sub-Saharan Africa in 2003-2015, but even in 2005, only 19.7% (95% confidence interval = 15.6-24.8) of children younger than 5 years with a fever and Plasmodium falciparum infection received an artemisinin-based combination therapy. In meta-analyses, children younger than 5 years were more likely to receive an artemisinin-based combination therapy for fever and Plasmodium falciparum infection if they lived in an urban area versus rural area (odds ratio = 1.18; 95% confidence interval = 1.16-1.39), had a household wealth above the national median versus wealth below the median (odds ratio =1.26; 95% confidence interval = 1.19-1.39) had a caregiver with any education versus no education (odds ratio = 1.31; 95% confidence interval = 1.22-1.41), had a household insecticide-treated

net insecticide-treated net versus no insecticide-treated net (odds ratio = 1.21; 95% confidence interval = 1.13-1.29), were older than 2 years versus ≤ 2 years (odds ratio = 1.09; 95% confidence interval = 1.01-1.17), or lived in an area with a higher Plasmodium falciparum prevalence in children for whom with a higher mean Plasmodium falciparum prevalence in children aged 2-10 years (odds ratio = 1.12; 95% confidence interval = 1.02-1.23). In the subgroup of children for whom treatment was sought, those who sought treatment in the public sector were more likely to receive an artemisinin-based combination therapy versus the private sector (odds ratio = 3.18; 95% confidence interval = 2.67-3.78). Despite progress during the 2003-2015 malaria programme artemisinin-based combination therapy treatment for children with malaria infection remains unacceptable low. More work is needed at the country level to understand how health-care access, service delivery, and artemisinin-based combination therapy supply might be improved to ensure appropriate treatment for all children with malaria infection.

The efficacy of intravenous quinine, which is the mainstay for treating severe malaria in children, is decreasing in South East Asia and Africa. Artemisinin derivatives are a potential alternative to quinine. However, their efficacy compared to quinine in treating severe malaria infection in children is not clearly understood. Praygod et al. (15) assessed the efficacy of parenteral artemisinin derivatives versus parenteral quinine in treating severe malarial infection in children. Twelve trials were included (1,524 subjects). There was no difference in mortality rate between artemisinin derivatives and quinine (relative risk = 0.90; 95% confidence interval = 0.73-1.12). The artemisinin derivatives resolved coma faster than quinine (weighted mean difference [WMD] = -4.61; 95% confidence interval = -7.21 to -2.00, fixed effect model), but when trials with adequate concealment only were considered this difference disappeared. There was no statistically significant difference between the two groups in parasite clearance time, fever clearance time, incidence of neurological sequelae and 28th day cure rate. One trial reported significantly more local reactions at the injection site with intramuscular quinine compared to artemether. None of the trials was adequately powered to demonstrate equivalence. There was no evidence that treatment of children with severe malarial infection with parenteral artemisinin was associated with lower mortality rate or long-term morbidity compared to parenteral quinine. Further studies require adequately powered equivalence trial design to decide whether both drugs are equally effective.

3-6. Treatment of malaria infection with artemisinin-based combination and other artemisinins in children

Artemisinin-based combination treatment has been widely adopted as one of the main malarial control strategies. However, its promise to save thousands of lives in sub-Saharan Africa depends on how effective the use of artemisinin-based combination treatment is within the routine health system. Timely access within 24 hours to an authorized artemisinin-based combination treatment outlet is one of the determinations of effective coverage and was assessed for artemether-lumefantrine, in two district health systems in rural Tanzania (16). Data were presented on timely access from a total of 2,122 interviews in relation to demographics, seasonality, and socio economics status. In Kilombero-Ulanga, 41.8% (95% confidence interval = 36.6 to 45.1), and in Rufiji 36.8% (95% confidence interval = 33.7 to 40.1) of fever cases had access to an authorized artemisinin-based

combination treatment provider within 24 hours of fever onset. In neither of the Health and Demographic Surveillance System Sites site was age, sex, socio-economic status or seasonality of malaria found to be significantly correlated with timely access. Timely access to authorized artemisinin-based combination treatment providers is below 50% despite interventions intended to improve access such as social marketing and accreditation of private dispending outlets. To improve diagnosis and treatment, access remains a major bottle neck and new more innovative interventions are needed to raise effective coverage of malaria treatment in Tanzania.

Despite recent improvements in malaria prevention strategies, malaria case management remain a weakness in Northern Nigeria, which is underserved and suffer the country's highest rates of under-five year- old children mortality rate (17). Overall, 76.7% of children were brought to treatment, 45.5% to a patent medicine vendor, and 43.8% to health facility. Of children brought to treatment, 61.5% sought treatment promptly, but only 9.8% received a diagnostic blood test and 7.2% received a prompt artemisinin-based combination therapy. When assessing adherence to the complete case management pathway, only 1.0% of children received Nigeria's National Control Programme and WHO recommended treatment. When compared to other treatment locations, health facilities provided the greatest proportion of children with Nigeria's National Control Programme and WHO recommended treatment. Lastly, children 7 to 59 months old were at 1.74 ($p = 0.003$) greater odds of receiving treatment than children ≤ 6 months. Northern Nigeria's coverage rates of Nigeria's National Control Programme and WHO recommended treatment standard malaria case management for children under five years with fever fall short of the Nigeria's National Control Programme goal of 80% coverage by 2010 and universal coverage thereafter. Given the ability to treat a child with malaria infection differs greatly between treatment locations, policy and logistics planning should address the shortages of essential malaria supplies in recommend and frequently accessed treatment locations. Particular emphasis should be placed on integrating the private sector into standardized care and educating caregivers on the necessity for testing before treatment and the availability of free artemisinin-based combination therapy in public health facilities for uncomplicated malaria infection.

The Roll Back Malaria strategy recommends a combination of interventions for malaria infection control. Zanzibar implemented artemisinin-based combination therapy for uncomplicated malarial infection in late 2003 and long-lasting insecticidal nets from early 2006 (18). Cross-sectional clinical and parasitological surveys in children under the age of 14 years were conducted in North A District in May 2003, 2005, and 2006. Survey data were analyzed in a logistic regression model and adjusted for complex sampling design and potential confounders. Records from 13 public health facilities in North A District were analyzed for malarial-related outpatients visits and admissions. Mortality rate and demographic data were obtained from District Commissioner's Office. Plasmodium falciparum prevalence decreased in children under five years old between 2003 and 2006; using 2003 as the reference year, (odds ratios = 0.55; 95% confidence intervals = 0.28-1.08) for 2005, and for 2006 (odds ratio = 0.03; 95% confidence interval = 0.00-0.27; p for trend < 0.001). Between 2002 and 2005 crude under-five years old, infant (under age of 1 year), and children (aged from 1 to 4 years old) mortality rate decreased by

52%, 33%, and 71%, respectively. Similarly, malaria-related admissions, blood transfusions, and malaria-attributed mortality rate decreased significantly by 77%, 67% and 75%, respectively, between 2002 and 2005 in children under five years old. Climatic conditions favorable for malaria transmission persisted throughout the observational period. Following deployment of artemisinin-based combination therapy in Zanzibar in 2003, malaria-associated morbidity and mortality decreased dramatically within two years.

Additional distribution of long-lasting insecticidal nets in early 2006 resulted in 10-fold reduction of malaria parasite prevalence. The results indicate that the Millennium Development Goals of reducing mortality rate in children less than five years of age and alleviating the burden of malaria are achievable in tropical Africa with high coverage of combined malaria control interventions.

New tools for malaria infection control, artemisinin-based combination therapy and long-lasting insecticidal nets were recently introduced across India. Shah et al. (19) estimated the impact of universal coverage of artemisinin-based combination therapy and artemisinin-based combination therapy plus long-lasting insecticidal nets in a setting of hyperendemic, forest malaria infection transmitted. During 2006 and 2009 malaria infection incidence per village ranged from 156 to 512 per 1,000 persons per year and slide prevalence ranged from 28 to 53%. Routine indoor residual spray did not prevent seasonal peaks of malaria infection. Post-intervention impact in 2010 and 2011 was decreased dramatically with ranges of 14 to 71 per 1,000 persons per year, and 6% to 16%, respectively. When adjusted for village, artemisinin-based combination therapy alone decreased the incidence of malaria by 83% (Relative risk = 0.17; 95% confidence interval = 0.05-0.38). After intervention, the age of malaria cases, their parasite density, and the proportion with fever at the time of screening increased. Artemisinin-based combination therapy, and long-lasting insecticidal nets along with artemisinin-based combination therapy, effectively reduced malaria incidence in a closely monitored population living in a forest ecotype. It is unclear whether long-lasting insecticidal nets were impactful when prompt and quality antimalarial treatment was available.

In 2004, Ghana implemented the artemisinin-based combination therapy policy. Health worker adherence to the national malaria guidelines on case-management with artemisinin-based combination therapy for children below 5 years of age and older children presenting at health facilities for primary illness consultations was evaluated 5 years post-artemisinin-based combination therapy policy change (20). Data from 130 health worker interviews, 769 patients' medical records at 20 health facilities over 75 survey days were individually linked and evaluated. The majority of consultations were performed at health centers/clinics (68.3%) by medical assistants (28.6%) and nurse aids (23.5%). About 68.4% of health workers had received artemisinin-based combination therapy-specific training and 51.9%, supervisory visits in the preceding 6 months. Despite the availability of malaria diagnostic tests at most health facilities (94%), only 241 (39.8%) out of 605 (78.7%) patients who reported fever were investigated for malaria infection. Treatment with artemisinin-based combination therapy in line with the guidelines was 66.7%; higher in < 5 years old children compared to children ≥ 5 years old. Judged against reference microscopy, only 44.8 % (107/239) of artemisinin-based combination prescriptions that conformed to the guidelines were "truly malaria". Multivariate logistic regression analysis

showed that health workers were significantly more likely to comply with the guidelines if treatment were by low cadre of health staff, were for children below 5 years of age, and malaria test was performed. Although the majority of patients presenting malaria infection received treatment according to the national malaria guidelines, there was widespread inappropriate treatment with artemisinin-based combination therapy. Compliance with the guidelines on artemisinin-based combination therapy use was low, 5 years post-artemisinin-based combination therapy policy change. The Ghana policy needs to strengthen health workers capacity on malaria case-management through regular training supported by effective laboratory quality control measures.

Effective case management of malaria infection requires prompt diagnosis and treatment within 24 hours. Home-based management of malaria infection improves access to treatment for populations with limited access to health facilities (21). From July 2009 through May 2010, 12,582 suspected cases were managed by Home Care Providers, 93% (111,672) of whom were tested with a rapid diagnostic test. Among those tested 37% (4,270) had a positive rapid diagnostic test, 97% (4,126) of whom were reported treated and cured. Home care providers referred 6,871 patients to health posts for management: 6,486 with a negative rapid diagnostic test, 119 infants < 2 months, 105 pregnant women, and 161 severe cases. There were no deaths among these patients. In 2009 compared to 2008, the incidence of in-hospital deaths due to malaria infection cases, all hospitalized and malaria-related hospitalizations decreased in both intervention and comparison regions. Incidence of in-hospital deaths due to malaria infection decreased by 62.5% (95% confidence interval = 43.8-81.2) in the intervention regions, while the decrease in comparison regions was smaller and not statistically significant. Home-based management of malaria infection including diagnosis with rapid diagnostic test and treatment based on test results is a promising strategy to improve the access of remote populations to prompt and effective management of uncomplicated malaria infection and to decrease mortality rate due to malaria infection. When scaled-up to severe remote village communities in the regions of Senegal with the highest malaria prevalence, home care providers demonstrated excellence adherence to guidelines, potentially contributing to a decrease in hospital deaths attributed to malaria infection.

Malaria-endemic countries are switching antimalarial drug policy to artemisinin combination therapies and the global community are considering the setting up of a global subsidy mechanism in order to make them accessible and affordable (13). However, specific interventions may be needed to reach remote at-risk communities and to ensure that they are used appropriately. This analysis documents the coverage with artemisinin-based combination therapies versus artemisinin monotherapies, and the effectiveness of malaria outreach teams and Village Malaria Workers in increasing access to appropriate diagnosis and treatment with artemisinin combination therapies in Cambodia, the first country to switch national antimalarial drug policy to an artemisinin-based combination therapy of artesunate and mefloquine. In areas without specific interventions, only 17% (42/251) of respondents received a biological diagnosis, 8% (17/206) of respondents who received modern drug did so from a public health facility, and only 8% (17/210) received artesunate and mefloquine. However, both the Village Malarial Work scheme and malaria outreach team scheme significantly

increased the likelihood of being seen by a trained provider (adjusted odds ratio of 148 and 4, respectively), and of receiving artesunate and mefloquine (adjusted odds ratios were = 2.7 and 7.7, respectively). The coverage rates of appropriate diagnosis and treatment of malaria were disappointing low and the use of artemisinin monotherapy alarming high. This reflects the fragmented nature of Cambodia's health system in remote areas and the reliance placed by these communities on informal vendors from whom artemisinin monotherapies are widely available. However, Village Malaria Workers in particular are an effective means of improving access to malaria diagnosis and treatment. The Village Malaria Worker scheme and the social marketing of rapid diagnostic tests and blister-packaged artesunate and mefloquine have both been scaled-up nationally. Case management in the public sector has also reportedly improved. Given recent concerns regarding the development of artemisinins drug resistance on the Thai-Cambodia border, the effectiveness of these measures in reducing the use of artemisinin monotherapy needs to be urgently re-evaluated.

Artemisinin-based combination therapy is the first-line treatment for malaria infection in most endemic countries and is increasingly available in the private sector. Most studies on artemisinin-based combination therapy adherence have been conducted in the public sector, with minimal data from private retailers (22). Parallel studies were conducted in Tanzania, in which patients obtaining artemether-lumefantrine at 40 randomly selected public health facilities and 37 accredited drug dispensing outlets were visited at home and questioned about doses taken. The effect of sector on adherence, controlling for potential confounders was assessed using logistic regression with a random effect for outlet. Of 572 health facility patients and 450 accredited drug dispensing outlet patients, 74.5% (95% confidence interval = 69.8-78.8), and 69.8% (95% confidence interval = 64.6-74.5), respectively, completed treatment and 46.0% (95% confidence interval = 40.9-51.2), and 34.8% (95% confidence interval = 30.1-39.8) took each dose at the correct time ("timely completion"). Accredited drug dispensing outlet patient were wealthier, more educated, older, sought care later in the day, and were less likely to test positive for malaria than health facility patients.

Controlling for patient characteristics were 0.65 (95% confidence interval = 0.43-1.00), and 0.69 (95% confidence interval = 0.47-1.01) times that of health facility patients. Higher socio-economic status was associated with both adherence measures. Higher education was associated with complete treatment (adjusted odds ratio = 1.68; 95% confidence interval = 1.20-2.36); obtaining artemether-lumefantrine in the evening was associated with timely completion (adjusted odds ratio = 0.35; 95% confidence interval = 0.19-0.64). Factors associated with adherence in each sector were examined separately. In health facility patients, but not accredited drug dispensing outlet patients, taking the first dose of artemether-lumefantrine at outlet was associated with timely completion (adjusted odds ratio = 2.11; 95% confidence interval = 1.46-3.04). When controlling for patient characteristics, there was some evidence that the adjusted odds of adherence for accredited drug dispensing outlet patients was lower than that for public health facility patients. Better understanding is needed of which patient care aspects are most important for adherence, including the role of effective provision of advice. Rectal administration of artemisinin derivatives has potential effect for early treatment for severe malarial infection in remote settings where injectable antimalarial therapy may not

feasible. Preparations available include artesunate, artemisinin, artemether, and dihydroartemisinin (23). However, each may have different pharmacokinetic properties and more information is needed to determine optimal dose and comparative efficacy with each another and with conventional parenteral treatments for severe malarial infection. The study was conducted in 1,167 patients in 15 clinical trials of rectal artemisinin derivative therapy (artesunate, artemisinin, and artemether) were pooled in order to compare the rapidity of clearance of Plasmodium falciparum parasitaemia and the incidence of reported adverse events with each treatment. Data from patients who received comparator treatment (parenteral artemisinin derivative or quinine) were also included. Primary endpoints included percentage reductions in parasitaemia at 12 and 24 hours.

A parasite reduction of > 90% at 24 hours was defined as parasitological success. Artemisinin and artesunate treatment cleared parasites more rapidly than parenteral quinine during the 24 hours of treatment. A single higher dose of rectal artesunate treatment was five times more likely to achieve > 90% parasite reduction at 24 hours than were multiple lower doses of rectal artesunate, or a single lower dose administration of rectal artemether. Artemisinin and artesunate suppositories rapidly eliminate parasites and appear to be safe. There are less data on artemether and dihydroartemisinin. This more rapid parasite clearance of single high-dose regimens suggests that achieving immediate high drug concentrations may be the optimal strategy.

3-7. Effects of artemisinin-based combination and other artemisinins in children

India contributes greatly to the global incidence of malarial infection. The factors influencing malaria infection in India are highly diverse and vary greatly from the epidemiological setting of any other country. Central India is the most vulnerably area for malarial infection in India (24). Singh et al. (24) carried out a study in three community health centers in Dindori District, Madhya Pradesh (Central India). Dindori District is mesoendemic for malarial infection, with both Plasmodium falciparum and Plasmodium vivax being present in all age groups. Anopheles culicifacies and Anopheles fluviatilis are highly efficient vectors of malaria. Singh et al. (2011) carried out an epidemic study of malarial infection among indigenous ethnic group Baigas to determine the causes of the epidemic and the population involved in order to aid in disease containment. The existence of sporozoites positive Anopheles culicifacies and Anopheles fluviatilis indicates either that spraying had not been done properly or the presence of insecticide resistant.

A combination of factors propagated the epidemic. Evidence suggests that the non-availability of artemisinin-based combination therapy and the rapid diagnostic tests along with an immunologically vulnerable population each played an important role. As the global prevalence of malarial infection decreases owing to initiatives to control or eliminate the disease, more areas will become hypoendemic and mesoendemic for malarial infection. Detection and control of epidemics requires greater attention, and mechanisms to ensure the quality of interventions are essential. Over the years, reports implicate improper anti-malarial use as a major contributor of morbidity and mortality amongst millions of residents in malaria endemic areas, Kenya included. However, there are limited reports on improper use of artemisinin-based combination therapy which is the first-line drug in the treatment of malarial infection in Kenya. Knowing this is important for ensured sustainable cure

rates and also protection against the emergence of resistant malarial parasites. Onyango et al. (25) therefore investigated the artemisinin-based combination therapy adherence level, factors associated with non-adherence and accessibility in households (N = 297) in rural location of Southeast Alego location in Siaya County in western Kenya.

Adherence to prescription remained low at 42.1% and 57.9% among individuals above 13 and less than 13 years old, respectively. Stratification by demographic and socio-economic characteristics in relation to artemisinin-based combination therapy adherence revealed that age ($p = 0.011$), education level ($p < 0.01$), ability to read ($p < 0.01$), and household monthly income ($p = 0.002$) significantly affected the level of artemisinin-based combination therapy adherence. Consistently, logistic regression model demonstrated that low age (odds ratio = 0.571; 95% confidence interval = 0.360-0.905; $p = 0.017$), higher education level (odds ratio = 0.074; 95% confidence interval = 0.017-0.322; $p < 0.01$), ability to read (odds ratio = 0.285; 95% confidence interval = 0.167-0.486; $p < 0.01$), and higher income (odds ratio = 0.340; 95% confidence interval = 0.167-0.694; $p = 0.003$) were associated with artemisinin-based combination therapy adherence. In addition, about 52.9% of the responders reported that artemisinin-based combination therapy was not always available at the source and that drug availability ($p = 0.020$) significantly affected accessibly. The present findings demonstrate that half of those who get artemisinin-based combination therapy prescription do not take recommended dose and that accessibly and also initiate programmatic interventions to encourage patient-centered care. Improving malaria case management is partially depended on health worker compliance with clinical guidelines. Selemani et al. (26) assessed health worker factors associated with correct anti-malarial prescribing practices at two sites in rural Tanzania. The analysis included 685 patients with uncomplicated malaria infection who were seen in a health facility with artemisinin-based combination therapy in stock, and 71 health workers practicing in 30 health facilities. Overall, 58% of malaria patients were correctly treated with artemisinin-based combination therapy.

Health workers with three or more years work experience were significantly more likely than others to prescribe correctly (adjusted odds ratio = 2.9; 95% confidence interval = 1.2-7.1; $p = 0.019$). Clinical officers (adjusted odds ratio = 2.2; 95% confidence interval = 1.1-4.5; $p = 0.037$), and nurse aide or lower cadre (adjusted odds ratio = 3.1; 95% confidence interval = 1.3-7.1; $p = 0.009$) were more likely to correctly prescribe artemisinin-based combination therapy than medical officers. Training on artemisinin-based combination therapy use, supervision visits, and available of job aids were not significantly associated with correct prescription. Years of working experience and health worker cadre were associated with correct artemisinin-based combination therapy prescription for uncomplicated malaria infection. Targeted interventions to improve health worker performance are needed to improve overall malaria case management.

Artemisinin-based combination therapy for treating malaria infection has activity against immune gametocytes. In theory, this property may complement the effect of terminating otherwise lengthy malaria infections and reducing the parasite reservoir in the human population that can infect vector mosquitoes. However, this has never been verified at a population level in a setting with intense transmission, where chronically infectious asymptomatic carriers are common and cured patients are rapidly and repeatedly re-infected (27). Plasmodium falciparum entomological

inoculation rates exceed 300 infective bites per person per year at both sites over the whole period. The introduction of artesunate plus sulphadoxine-pyrimethamine in Rufiji was associated with increased oocyst prevalence (odds ratio = 3.9; 95% confidence interval = 2.9-5.3; p = 0.5). The estimated infectiousness of the human population in Rufiji was very low prior to the change in drug policy. Emergence rates and parous rates of the vectors varied substantially throughout the study period, which affected estimates of infectiousness. The latter consequently cannot be explained by the change in drug policy. In high perennial transmission settings, only a small proportion of infections in humans are symptomatic or treated, so case management with an artemisinin-based combination therapy may have little impact on overall infectiousness on the human population. Variations in infection levels in vectors largely depend on the age distribution of the mosquito population. Benefits of artemisinin-based combination therapy in suppressing transmission are more likely to be evident where transmission is already low or effective vector control is widely implemented.

3-8. Resistance of Plasmodium parasites to artemisinin-based combination and other artemisinins in children

Resistance to anti-malarial chemotherapy is a major concern for malaria control in Viet Nam. A study undertaken in 1998, 65 patients with uncomplicated falciparum malaria infection were monitored for 28 days after completion of a 5 day treatment course with artemisinin (28). Overall 36.9% (24/65) of patients had recurrent parasitaemia during the surveillance period. Plasmodium falciparum isolates were tested for sensitivity in-vitro to chloroquine, mefloquine, quinine, and sulfadoxine-pyrimethamine and results were compared to those from a similar study in 1995. Increased parasite sensitivity to sulfadoxine-pyrimethamine, chloroquine and quinine was demonstrated; with significantly lower mean half maximal effective concentration (EC50), and EC_{99} values in 1998 compared to 1995. Parasite sensitivity to mefloquine did not differ significantly in the 2 surveys. Isolates were also tested for sensitivity in-vitro to artemisinin in the 2008 survey. The mean EC_{50} was 0.03μmol/l and the EC_{99} was 0.94μmol/l. Parasite sensitivity to artemisinin will need to be monitored in view of its increasing use in Vietnam.

Artemisinin do not display significant clinical cross-resistance with other drugs. Indeed, sensitive to artemisinin may be increases in at least some strains of chloroquine-resistant parasites. Dondorp et al. (29) studied 40 patients in each of the two locations. The overall median parasite clearance times were 84 hours (interquartile range, 60 to 96) in Pailin and 48 hours (interquartile range, 36 to 66) in Wang Pha (P<0.001). Recrudescence confirmed by means of PCR assay occurred in 6 of 20 patients (30%) receiving artesunate monotherapy and 1 of 20 (5%) receiving artesunate-mefloquine therapy in Pailin, as compared with 2 of 20 (10%), and 1 of 20 (5%), respectively, in Wang Pha (P=0.31). These markedly different parasitological responses were not explained by differences in age, artesunate or dihydroartemisinin pharmacokinetics, results of isotopic in-vitro sensitivity tests, or putative molecular correlates of Plasmodium falciparum drug resistance (mutations or amplifications of the gene encoding a multidrug resistance protein or mutations in the gene encoding sarco-endoplasmic reticulum calcium ATPase6). Adverse events were mild and did not differ significantly between the two treatment groups. Plasmodium falciparum has reduced in-vivo susceptibility to artesunate in western Cambodia as compared with northwestern Thailand.

Resistance is characterized by slow parasite clearance in-vivo without corresponding reductions on conventional in vitro susceptibility testing. Containment measures are urgently needed.

The area along the Thai-Cambodian is considered an epicenter of anti-malarial resistance (30). Recently, parasite resistance to artemisinin-based therapies has been reported in the area. The artemisinin resistance containment project was initiated in November 2008, with the limit resistant parasites and eliminates malaria in this region. A total of 1,709 Plasmodium falciparum-positive individuals were reported during the study period. Almost 70% of falciparum cases received mefloquine-artesunate combination therapy (N = 1,174).

The majority of cases were males, aged between 31 and 50 years. The overall mefloquine-artesunate combination therapy cure rate was > 90% over the three-year period. Almost 14% of patients undergoing mefloquine-artesunate combination therapy remained parasite-positive on day 3. Delayed parasite clearance was not significantly associated with patient gender, age, or citizenship. However, delayed parasite clearance varied across the study area. Anti-malarial drug-resistant parasites should be closely monitored in the area along the Thai-Cambodian border. Although the mefloquine-artesunate combination therapy cure rate in this study area neighboring parts. Effective malarial surveillance is an important component to monitor drug-resistance in the malaria component project. In Cambodia, elimination of artemisinin resistance through direct elimination of the Plasmodium falciparum parasite may be the only strategy (31). District Plasmodium falciparum prevalence was 0.74%. The annual incidence of Plasmodium falciparum was 16.8 cases per 1,000 inhabitants in the district of Chey Saen in North, Cambodia; village incidence ranged from 1.3 to 54.9 for 1,000 inhabitants. The marker for artemisinin resistance was found in 6 samples out of the 11 tested (55%). The overall low prevalence of Plasmodium falciparum prevalence was of 0.74 % (range, 0.41; 1.21); village prevalence ranged from 0 to 4.6 % (range, 1.4; 10.5). The annual incidence of Plasmodium falciparum was 16.8 cases per 1000 inhabitants in the district; village incidence ranged from 1.3 to 54.9 for 1000 inhabitants. Two geographical clusters with high number of cases were identified by both approaches. A percentage of 34.9 of real-time PCR (qPCR) blood analysis of symptomatic patients were still positive at D-28. The overall low prevalence of Plasmodium falciparum was confirmed in Chey Saen district in Cambodia, while there were important variations between villages. Symptomatic cases had a different pattern and were likely acquired outside the villages.

It illustrates the importance of prevalence surveys in targeting interventions for elimination. Mutations in the k13-propeller domain gene (C580Y), conferring artemisinin resistance, were highly prevalent in both symptomatic and asymptomatic cases (realizing the absolute figures remain low). Asymptomatic individuals could be an additional reservoir for artemisinin resistance. The low effectiveness of dihydroartemisinin-piperaquine for symptomatic cases indicates that piperaquine (PPQ) is no longer able to complement the reduced potency of dihydroartemisinin (DHA) to treat falciparum malaria and highlights the need for an alternative first-line treatment. Intensified efforts are urgently need to contain and eliminate artemisinin-resistant Plasmodium falciparum in the Greater Mekong subregion (32). Medicines Sans Frontier plans to support the Ministry of Health in eliminating Plasmodium falciparum in an area with artemisinin

resistance in the north-east Cambodia. The prevalence of Plasmodium species was estimated at 1.49% (95% confidence interval = 0.71 to 3.11%) in Chhaeb and 2.61% (95% confidence interval = 1.45 to 4.66%) in Chey Saen. Twenty-seven samples were positive for Plasmodium falciparum, giving a prevalence of 0.16% (95% confidence interval = 0.04-0.65) in Chhaeb, and 2.04% (95% confidence interval = 1.04-3.99%) in Chey Saen. Only 4.0% of the participants testing positive presented with fever or history of fever. The kelch 13 (K13) propeller domain mutant type alleles (C580Y and Y493H) were found, only in Chey Saen district, in seven out of 11 Plasmodium falciparum positive samples with enough genetic material to allow testing.

Confirmation of artemisinin-delayed parasite clearance in Plasmodium falciparum along the Thai-Myanmar border has inspired a global response to contain and monitor drug resistance to avert the disastrous consequences of a potential spread to Africa. However, resistance where limited health services and decades of displacement create conditions for resistance genes that confer fitness disadvantages relative to wild-type alleles. The present findings estimate the prevalence of resistance genotypes in 3 previously unstudied remote populations in Myanmar and test the a priori hypothesis that resistance gene prevalence would be higher among isolates collected from subclinical infections than isolates collected from febrile clinical patients. A systematic review of resistance studies is provided for context (33). Pfmdr1 copy number increase was present in 17.5%, 9.6% and 11.1% of isolates from Karen and Kachin States and the Indo-Myanmar border, respectively. Pfmdr1 amplification was more prevalent in subclinical isolates (20.3%) than clinical isolates (6.4%, odds ratio = 3.7, 95% confidence interval = 1.1 - 12.5). The P. falciparum chloroquine resistance transporter (Pfcrt) K76T prevalence ranged from 90 to 100%. Community health workers can contribute to molecular surveillance of drug resistance in remote areas of Myanmar. Marginal and displaced populations under-represented among previous resistance investigations can and should be included in resistance surveillance efforts, particularly once genetic markers of artemisinin-delayed parasite clearance are identified. Subclinical infections may contribute to the epidemiology of drug resistance, but determination of gene amplification from desiccated filter samples requires further validation when DNA concentration is low.

Substantial reductions in malaria infection have been reported in several African countries after distribution of insecticide-treated bed-nets and the use of artemisinin-based combination therapies (34). Trape et al. (34) did a longitudinal study of inhabitants in Dielmo village, Senegal, between January, 2007, and December, 2010. These authors monitored the inhabitants for fever during this period and treated malaria attacks with artesunate plus amodiaquine. In July 2008, they offered long-lasting insecticide-treated nets to all villagers. They did monthly night collections of mesquites during the whole study period, and assessed asymptomatic carriage from cross-sectional surveys. The incidence density of malaria attacks averaged 5.45 per 100 persons-months between January 2007 and July 2008, before the distribution of long-lasting insecticide-treated nets. Incidence density decreased to 0.41 (0.95 to 0.55) between August 2008 and August 2010, but increases back to 4.57 (3.54 to 5.82) between September and December 2010 - i.e. 27 months after the distribution of long-lasting insecticidal nets (LLINs). The rebound of malaria attacks was highest in adults and children aged 10 years or older: 45 (63%) of 71 malaria attacks recorded in

2010 compared with 126 (33%) of 384 in 2007 and 2008 ($p < 0.0001$). A percentage of 37 of Anopheles gambiae mosquitoes were resistant to deltamethrin in 2010, and the prevalence of the leucine to phenylalanine substitution (Leu1014Phe) kdr resistant mutation increased from 8% in 2007 to 48% in 2010 ($p = 0.0009$). Increasing pyrethroid resistance of Anopheles gambiae (An. Gambiae), and increasing susceptibility of older children and adults, probably due to decreased immunity, caused insecticide resistance and to mitigate its effects must be urgently defined and implemented. Regular monitoring of the level of anti-malarial resistance of Plasmodium falciparum is an essential policy to adapt therapy and improve malaria control (35). This monitoring can be facilitated by using molecular tools, which are easier to implement than the classical determination of the resistance phenotype. In Cameroon, chloroquine, previously the first-line therapy for uncomplicated malaria infection was officially withdrawn in 2002 and replaced initially by amodiaquine monotherapy. Then, artemisinin-based combination therapy, notably artesunate-amodiaquine or artemether-lumefantrine was gradually introduced in 2004. This situation raised the question of the evolution of Plasmodium falciparum resistance molecular markers in Yaoundè, a highly urbanized Cameroonian city. The high prevalence of mutant pfcrt 76T and pfmdr1 86Y alleles might be due to the choice of alternative drugs (amodiaquine and artesunate-amodiaquine) known to select such genotypes. Mutant pfcrt 72 codon was no detected despite the prolonged use of amodiaquine either as monotherapy or combined with artesunate. The absence of pfmdr1 multicopies suggests that artemether-lumefantrine would still remain efficient. The limited use of mefloquine or the predominance of mutant pfmdr1 86Y codon could explain the lack of pfmdr1 amplification; in Cameroon, the changes of therapeutic strategies and the simultaneous use of several formulations of artemisinin-based combination therapy or other anti-malarias that are not officially recommended result in a complex selective pressure, rendering the prediction of the evolution of Plasmodium falciparum resistance difficult. This public health problem should lead to increased vigilance and regular monitoring.

4- DISCUSSION

The artemisinins are very potent and fast-acting antimalarials, including more rapid parasite clearance and fever resolution than any other currently licensed antimalarial drugs. They are particularly well suited for the treatment of severe Plasmodium falciparum malaria and are also affected against the asexual erythrocytic stages of Plasmodium vivax. Increasingly, the standard treatment of malaria employs artemisinin-based combination therapies to increase treatment efficacy and reduce selection pressure for drug resistance (1). Artemisinins cause a significant reduction of the parasite burden. Only three to four cycles (6 to 8 days) of treatment are required to remove all the parasites from the blood (3). Additionally, artemisinins possess some gametocytocidal activity, leading to a decrease in malaria parasite transmission. Artemisinin-based combination therapy has low toxicity and is considered safe for use in nonpregnant adults and children. The children are more vulnerable than adults to Plasmodium parasites (1).

Semisynthetic artemisinins have been formulated for oral (dihydroartemisinin, artesunate, and artemether), intramuscularly (artesunate and artemether), intravenous (artesunate), and rectal (artesunate) administration (1). Bioavailability after oral dosing typically is $\leq$ 30%. Rectal administration of

artesunate has emerged as an important administration route especially in tropical countries where it can be lifesaving. However, drug bioavailability via rectal administration is highly variable among individual patients (5). Malaria affects about a quarter of a billion people and leads to almost 900,000 deaths annually (WHO 2009). This disease is caused by infections with single-celled protozoan parasites of the genus Plasmodium. Five Plasmodium species are known to infect humans: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi. Plasmodium falciparum and Plasmodium vivax cause most of the malarial infections worldwide; of these, Plasmodium falciparum accounts for the majority of the burden of malaria infection in sub-Sahara African countries and is associated with most severe disease. Plasmodium vivax accounts for half of the malarial burden in South and East Asia and > 80% of the malarial infections in the America (1).

A pilot programme of Cohort Event Monitoring was conducted across the six geopolitical zones of Nigeria on patients treated for uncomplicated malaria infection with artemisinin-based combination therapy. The emergence and spread of malarial parasites resistance to commonly available antimalarial drugs necessitated a shift in policy for malaria treatment by the Federal Government from the use of chloroquine and sulphadoxine-pyrimethamine as first-line treatment to artemisinin-based combination. Although artemisinin and derivatives are generally thought to be save, but there are currently few or no data on their safety among population of Nigeria. Adverse events were more common in the Artesunate/amodiaquine group than artemether-lumefantrine revealing a better safety profile for artemether/lumefantrine ($p < 0.001$). Artemisinin-based combination therapy demonstrated good ability to resolve the clinical symptoms of uncomplicated malaria infection (6). An increasing number of countries in sub-Saharan Africa are changing to artemisinins combination therapy as first or second line treatment for malarial infection. There is an urgent need to assess the safety of these drugs in pregnant women who may be inadvertently exposed to or actively treated with artemisinin-based combination therapies (7). The primary endpoints for these studies were drug efficacy and parasite clearance. Secondary endpoints were birth weight, pre-term birth, pregnancy loss, congenital anomalies and developmental milestone. The use of drug combinations, including non-artemisinin-based and artemisinin-based combination therapy, is a novel strategy that enhances therapeutic efficacy and delays the emergence of multiple-resistant Plasmodium falciparum (9).

Its use is strongly recommended in most sub-Saharan African countries, namely Cameroon, where resistant to chloroquine is widespread and antifolate resistance is emerging. The results based on the meta-analysis suggested that artesunate-amodiaquine is as effective as other drugs (artesunate-sulphadoxine-pyrimethamine, artesunate-chlorproguanil-dapsone, artesunate-mefloquine, dihydroartemisinin-piperaquine, artemether-lumefantrine, amodiaquine, and amodiaquine-sulphadoxine-pyrimethamine).

Although artemether-lumefantrine requires six doses, rather than three doses for artemisinin-based combinations, it has potential advantages over other forms of artemisinin-based combination therapy. Artesunate plus sulfadoxine-pyrimethamine and artemether plus lumefantrine are the first- and second line treatments, respectively, for the treatment of Plasmodium falciparum infections and

dihydroartemisinin plus piperaquine is a potential candidate in case artesunate plus sulfadoxine-pyrimethamine or artemether plus lumefantrine fails in Pakistan (10). Artesunate plus pyrimethamine remains highly effective in Pakistan. New malaria infection guidelines in Tanzania have led to the large-scale development of artemether-lumefantrine (Coartem), popularly known as ALu or dawa mseto. Very little is known about how people in malaria endemic areas interpret policy markers' decision to replace existing anti-malarials, such as sulphadoxine-pyrimethamine with "new" treatment regimens, such as ALu or other formulations of artemisinin-based combination therapy (11).

Development of ALu has significantly changed community level perceptions of anti-malarial treatment. However, mothers continue to delay seeking care before accessing ALu, limiting the impact of highly subsidized rollout of the drug. Implementation of artemisinin-based combination treatment guidelines must be complemented with educational campaigns to insure that mothers seek prompt help for their children within 24 hours of the onset of fever. Following the development of resistance to anti-malaria mono-therapies, malaria endemic countries in Africa now use artemisinin-based combination therapy as recommended the first-line treatment for uncomplicated malaria infection. Patients' adherence to artemisinin-based combination therapy is an important factor to ensure treatment efficacy, as well as to reduce the likelihood of parasite resistance to these drugs. Lawford et al. (12) report adherence to a specific artemisinin-based combination therapy, under conditions of routine clinical practice in Kenya. Malaria-endemic countries are switching antimalarial drug policy to artemisinin-based combination therapies and the global community is considering the setting up of a global subsidy mechanism in order to make them accessible and affordable. However, specific interventions may be needed to reach remote at-risk communities and to ensure that they are used appropriately (13). This analysis documents the coverage with artemisinin-based combination therapies versus artemisinin monotherapies, and the effectiveness of malaria outreach teams and Village Malaria Workers in increasing access to appropriate diagnosis and treatment with artemisinin-based combination therapies in Cambodia, the first country to switch national antimalarial drug policy to an artemisinin-based combination therapy of artesunate and mefloquine in 2000. Lawford et al. (12) report adherence to a specific artemisinin-based combination therapy, under conditions of routine clinical practice in Kenya. Despite recent improvements in malaria prevention strategies, malaria case management remains a weakness in Northern Nigeria, which is underserved and suffers the countries with highest rates of under-five year- old children mortality rate (17). Overall, 76.7% of children were brought to treatment, 45.5% to a patent medicine vendor, and 43.8% to health facility. Of children brought to treatment, 61.5% sought treatment promptly, but only 9.8% received a diagnostic blood test and 7.2% received a prompt artemisinin-based combination therapy.

Following deployment of artemisinin-based combination therapy in Zanzibar in 2003, malaria-associated morbidity and mortality decreased dramatically within two years. Additional distribution of long-lasting insecticidal nets in early 2006 resulted in 10-fold reduction of malaria parasite prevalence. Particular emphasis should be placed on integrating the private sector into standardized care and educating caregivers on the necessity for testing before treatment and the availability of free artemisinin-based combination therapy in public health facilities for

uncomplicated malaria infection. Artemisinin-based combination therapies are the most effective treatment for uncomplicated Plasmodium falciparum malaria infection. A commonly used indicator for monitoring and assessing progress in coverage of malarial infection treatment is the proportion of children younger than 5 years with reported fever in the previous 14 days who have received artemisinin-based combination therapy (14). The present findings showed that artemisinin-based combination therapy coverage in children younger than 5 years old with a fever and Plasmodium falciparum infection increased across sub-Saharan African countries in 2003-2015, but even in 2005, only 19.7% of children younger than 5 years with a fever and Plasmodium falciparum infection received an artemisinin-based combination therapy. Despite progress during the 2003-2015 malaria programme, artemisinin-based combination therapy treatment for children with malaria infection remains unacceptable low. More work is needed at the country level to understand how health-care access, service delivery, and artemisinin-based combination therapy supply might be improved to ensure appropriate treatment for all children with malaria infection.

The efficacy of intravenous quinine, which is the mainstay for treating severe malaria in children, is decreasing in South East Asia and Africa. Artemisinin derivatives are a potential alternative to quinine. However, their efficacy compared to quinine in treating severe malaria infection in children is not clearly understood. Praygod et al. (15) assessed the efficacy of parenteral artemisinin derivatives versus parenteral quinine in treating severe malarial infection in children. Twelve trials were included (1,524 subjects). There was no difference in mortality rate between artemisinin derivatives and quinine. The artemisinin derivatives resolved coma faster than quinine, but when trials with adequate concealment only were considered this difference disappeared. There was no statistically significant difference between the two groups in parasite clearance time, fever clearance time, incidence of neurological sequelae and 28th days cure rate. One trial reported significantly more local reactions at the injection site with intramuscular quinine compared with artemether. There was no evidence that treatment of children with severe malarial infection with parenteral artemisinin was associated with lower mortality rate or long-term morbidity compared to parenteral quinine.

Artemisinin-based combination treatment has been widely adopted as one of the main malarial control strategies. However, its promise to save thousands of lives in sub-Saharan Africa depends on how effective the use of artemisinin-based combination treatment is within the routine health system. Timely access within 24 hours to an authorized artemisinin-based combination treatment outlet is one of the determinations of effective coverage and was assessed for artemether-lumefantrine, in two district health systems in rural Tanzania [16]. Data were presented on timely access from a total of 2,122 interviews in relation to demographics, seasonality, and socio economics status. In Kilombero-Ulanga, 41.8% and in Rufiji 36.8% of fever cases had access to an authorized artemisinin-based combination treatment provider within 24 hours of fever onset. Zanzibar implemented artemisinin-based combination therapy for uncomplicated malarial infection in late 2003 and long-lasting insecticidal nets from early 2006 (18). Cross-sectional clinical and parasitological surveys in children under the age of 14 years were conducted in North A District in May 2003, 2005, and 2006. Survey data were analyzed in a logistic regression model and adjusted for complex sampling design and

potential confounders. Records from 13 public health facilities in North A District were analyzed for malarial-related outpatients visits and admissions. Plasmodium falciparum prevalence decreased in children less than five years old between 2003 and 2006. Between 2002 and 2005 crude under-five years old, infant (under age of 1 year), and children (aged from 1 to 4 years old) mortality rate decreased by 52%, 33%, and 71%, respectively.

New tools for malaria infection control, artemisinin-based combination therapy and long-lasting insecticidal nets were recently introduced across India. Shah et al. (19) estimated the impact of universal coverage of artemisinin-based combination therapy and artemisinin-based combination therapy plus long-lasting insecticidal nets in a setting of hyperendemic, forest malaria infection transmitted. During 2006 and 2009 malaria infection incidence per village ranged from 156 to 512 per 1,000 persons per year and slide prevalence ranged from 28 to 53. Post-intervention impact in 2010 and 2011 was decreased dramatically with ranges of 14 to 71 per 1,000 persons per year, and 6% to 16%, respectively. When adjusted for village, artemisinin-based combination therapy alone decreased the incidence of malaria by 83%. Artemisinin-based combination therapy and long-lasting insecticidal nets along with artemisinin-based combination therapy effectively reduced malaria incidence in a closely monitored population living in a forest ecotype. In 2004, Ghana implemented the artemisinin-based combination therapy policy. Health worker adherence to the national malaria guidelines on case-management with artemisinin-based combination therapy for children below 5 years of age and older children presenting at health facilities for primary illness consultations was evaluated 5 years post-artemisinin-based combination therapy policy change (20). The majority of consultations were performed at health centers/clinics (68.3%) by medical assistants (28.6%) and nurse aids (23.5%). About 68.4% of health workers had received artemisinin-based combination therapy-specific training and 51.9%, supervisory visits in the preceding 6 months. Treatment with artemisinin-based combination therapy in line with the guidelines was 66.7% higher in < 5 years old children compared to children ≥ 5 years old. Compliance with the guidelines on artemisinin-based combination therapy use was low, 5 years post-artemisinin-based combination therapy policy change. The Ghana policy needs to strengthen health workers capacity on malaria case-management through regular training supported by effective laboratory quality control measures.

Effective case management of malaria infection requires prompt diagnosis and treatment within 24 hours. Home-based management of malaria infection improves access to treatment for populations with limited access to health facilities (21). Home-based management of malaria infection including diagnosis with rapid diagnostic test and treatment based on test results is a promising strategy to improve the access of remote populations to prompt and effective management of uncomplicated malaria infection and to decrease mortality rate due to malaria infection. When scaled-up to severe remote village communities in the regions of Senegal with the highest malaria prevalence, home care providers demonstrated excellence adherence to guidelines, potentially contributing to a decrease in hospital deaths attributed to malaria infection. Malaria-endemic countries are switching antimalarial drug policy to artemisinin combination therapies and the global community are considering the setting up of a global subsidy mechanism in order to make them accessible and affordable (13). However,

specific interventions may be needed to reach remote at-risk communities and to ensure that they are used appropriately. This analysis documents the coverage with artemisinin-based combination therapies versus artemisinin monotherapies. Case management in the public sector has also reportedly improved. Given recent concerns regarding the development of artemisinins drug resistance on the Thai-Cambodia border, the effectiveness of these measures in reducing the use of artemisinin monotherapy needs to be urgently re-evaluated.

Artemisinin-based combination therapy is the first-line treatment for malaria infection in most endemic countries and is increasingly available in the private sector. Most studies on artemisinin-based combination therapy adherence have been conducted in the public sector, with minimal data from private retailers (22). Parallel studies were conducted in Tanzania, in which patients obtaining artemether-lumefantrine at 40 randomly selected public health facilities and 37 accredited drug dispensing outlets were visited at home and questioned about doses taken. Rectal administration of artemisinin derivatives has potential effect for early treatment for severe malarial infection in remote settings where injectable antimalarial therapy may not feasible. Preparations available include artesunate, artemisinin, artemether, and dihydroartemisinin (23). However, each may have different pharmacokinetic properties and more information is needed to determine optimal dose and comparative efficacy with each another and with conventional parenteral treatments for severe malarial infection. Primary endpoints included percentage reductions in parasitaemia at 12 and 24 hours. A parasite reduction of > 90% at 24 hours was defined as parasitological success. Artemisinin and artesunate treatment cleared parasites more rapidly than parenteral quinine during the 24 hours of treatment. A single higher dose of rectal artesunate treatment was five times more likely to achieve > 90% parasite reduction at 24 hours than were multiple lower doses of rectal artesunate, or a single lower dose administration of rectal artemether. Artemisinin and artesunate suppositories rapidly eliminate parasites and appear to be safe. Central India is the most vulnerably area for malarial infection in India (24). Singh et al. (24) carried out a study in three community health centers in Dindori District, Madhya Pradesh (Central India). Dindori District is mesoendemic for malarial infection, with both Plasmodium falciparum and Plasmodium vivax being present in all age groups. Anopheles culicifacies and Anopheles fluviatilis are highly efficient vectors of malaria. Evidence suggests that the non-availability of artemisinin-based combination therapy and the rapid diagnostic tests along with an immunogenically vulnerable population each played an important role.

Over the years, reports implicate improper anti-malarial use as a major contributor of morbidity and mortality amongst millions of residents in malaria endemic areas, Kenya included. However, there are limited reports on improper use of artemisinin-based combination therapy which is the first-line drug in the treatment of malarial infection in Kenya (25). The present findings demonstrate that half of those who get artemisinin-based combination therapy prescription do not take recommended dose and that accessibly and also initiate programmatic interventions to encourage patient-centered care. Selemani et al. (26) assessed health worker factors associated with correct anti-malarial prescribing practices at two sites in rural Tanzania. The analysis included 685 patients with uncomplicated malaria infection who were seen in a health facility with artemisinin-based combination therapy in stock, and 71 health workers

practicing in 30 health facilities. Overall, 58% of malaria patients were correctly treated with artemisinin-based combination therapy. Training on artemisinin-based combination therapy use, supervision visits, and available of job aids were not significantly associated with correct prescription. Years of working experience and health worker cadre were associated with correct artemisinin-based combination therapy prescription for uncomplicated malaria infection.

Artemisinin-based combination therapy for treating malaria infection has activity against immune gametocytes (27). Plasmodium falciparum entomological inoculation rates exceed 300 infective bites per person per year at both sites over the whole period. In high perennial transmission settings, only a small proportion of infections in humans are symptomatic or treated, so case management with an artemisinin-based combination therapy may have little impact on overall infectiousness on the human population. Benefits of artemisinin-based combination therapy in suppressing transmission are more likely to be evident where transmission is already low or effective vector control is widely implemented. Resistance to anti-malarial chemotherapy is a major concern for malaria control in Vietnam. A study undertaken in 1998, 65 patients with uncomplicated falciparum malaria infection were monitored for 28 days after completion of a 5 day treatment course with artemisinin (28). Overall 36.9% (24/65) of patients had recurrent parasitaemia during the surveillance period. Artemisinin do not display significant clinical cross-resistance with other drugs. Indeed, sensitive to artemisinin may be increases in at least some strains of chloroquine-resistant parasites. Dondorp et al. (29) studied 40 patients the overall median parasite clearance times were 84 hours in Pailin and 48 hours in Wang Pha (P<0.001). Plasmodium falciparum has reduced in-vivo susceptibility to artesunate in western Cambodia as compared with northwestern Thailand. Resistance is characterized by slow parasite clearance in-vivo without corresponding reductions on conventional in-vitro susceptibility testing. Containment measures are urgently needed. The area along the Thai-Cambodian is considered an epicenter of anti-malarial resistance (30). Recently, parasite resistance to artemisinin-based therapies has been reported in the area. The artemisinin resistance containment project was initiated in November 2008, with the limit resistant parasites and eliminates malaria in this region. A total of 1,709 Plasmodium falciparum-positive individuals were reported during the study period. However, delayed parasite clearance varied across the study area and the anti-malarial drug-resistant parasites should be closely monitored in the area along the Thai-Cambodian border. Although the mefloquine-artesunate combination therapy cure rate in this study area neighboring parts. Effective malarial surveillance is an important component to monitor drug-resistance in the malaria component project.

In Cambodia, elimination of artemisinin resistance through direct elimination of the Plasmodium falciparum parasite may be the only strategy (31). District Plasmodium falciparum prevalence was 0.74%. The annual incidence of Plasmodium falciparum was 16.8 cases per 1,000 inhabitants in the district of Chey Saen in North, Cambodia; village incidence ranged from 1.3 to 54.9 for 1,000 inhabitants. The marker for artemisinin resistance was found in 6 samples out of the 11 tested (55%). The overall low prevalence of Plasmodium falciparum was confirmed in Chey Saen district in Cambodia, while there were important variations between villages. Symptomatic cases had a

different pattern and were likely acquired outside the villages. It illustrates the importance of prevalence surveys in targeting interventions for elimination. Mutations in the k13-propeller domain gene (C580Y), conferring artemisinin resistance, were highly prevalent in both symptomatic and asymptomatic cases. Asymptomatic individuals could be an additional reservoir for artemisinin resistance. Intensified efforts are urgently need to contain and eliminate artemisinin-resistant Plasmodium falciparum in the Greater Mekong sub-region (32). Medicines Sans Frontier plans to support the Ministry of Health in eliminating Plasmodium falciparum in an area with artemisinin resistance in the north-east Cambodia. The prevalence of Plasmodium species was estimated at 1.49 in Chhaeb and 2.61% in Chey Saen. Twenty-seven samples were positive for Plasmodium falciparum, giving a prevalence of 0.16% in Chhaeb and 2.04% in Chey Saen.

Only 4.0% of the participants testing positive presented with fever or history of fever. K13-propeller domain mutant type alleles (C580Y and Y493H) were found, only in Chey Saen district; in seven out of 11 (55%), Plasmodium falciparum positive samples with enough genetic material to allow testing. Confirmation of artemisinin-delayed parasite clearance in Plasmodium falciparum along the Thai-Myanmar border has inspired a global response to contain and monitor drug resistance to avert the disastrous consequences of a potential spread to Africa. However, resistance where limited health services and decades of displacement create conditions for resistance genes that confer fitness disadvantages relative to wild-type alleles. A systematic review of resistance studies is provided for context [33]. Pfmdr1 copy number increase was present in 17.5%, 9.6% and 11.1% of isolates from Karen and Kachin States and the Indo-Myanmar border, respectively. Pfmdr1 amplification was more prevalent in subclinical isolates (20.3%) than clinical isolates (6.4%). Pfcrt K76T prevalence ranged from 90 to 100%. Community health workers can contribute to molecular surveillance of drug resistance in remote areas of Myanmar. Marginal and displaced populations under-represented among previous resistance investigations can and should be included in resistance surveillance efforts, particularly once genetic markers of artemisinin-delayed parasite clearance are identified.

Substantial reductions in malaria infection have been reported in several African countries after distribution of insecticide-treated bed-nets and the use of artemisinin-based combination therapies (34). Trape et al. (34) did monthly night collections of mesquites during the whole study period, and assessed asymptomatic carriage from cross-sectional surveys. The rebound of malaria attacks was highest in adults and children aged 10 years or older.

A percentage of 37 of Anopheles gambiae mosquitoes were resistant to deltamethrin in 2010, and the prevalence of the Leu1014Phe kdr resistant mutation increased from 8% in 2007 to 48% in 2010 ($p = 0.009$). Regular monitoring of the level of anti-malarial resistance of Plasmodium falciparum is an essential policy to adapt therapy and improve malaria control (35). This monitoring can be facilitated by using molecular tools, which are easier to implement than the classical determination of the resistance phenotype. In Cameroon, chloroquine, previously the first-line therapy for uncomplicated malaria infection was officially withdrawn in 2002 and replaced initially by amodiaquine monotherapy. Then, artemisinin-based combination therapy, notably artesunate-amodiaquine or artemether-lumefantrine was gradually introduced in 2004. This situation raised the question of the evolution of Plasmodium falciparum resistance

molecular markers in Yaoundè, a highly urbanized Cameroonian city. The high prevalence of mutant pfcrt 76T and pfmdr1 86Y alleles might be due to the choice of alternative drugs (amodiaquine and artesunate-amodiaquine) known to select such genotypes. Mutant pfcrt 72 codon was no detected despite the prolonged use of amodiaquine either as monotherapy or combined with artesunate. The absence of pfmdr1 multicopies suggests that artemether-lumefantrine would still remain efficient. In Cameroon the changes of therapeutic strategies and the simultaneous use of several formulations of artemisinin-based combination therapy or other anti-malarias that are not officially recommended result in a complex selective pressure, rendering the prediction of the evolution of Plasmodium falciparum resistance difficult. This public health problem should lead to increased vigilance and regular monitoring. There is the need to carry out an international survey to establish the best artemisinin to act against the Plasmodium parasites.

5- CONCLUSION

In conclusion, malaria affects about a quarter of a billion people and leads to almost 900,000 deaths annually (WHO 2009). There are five parasites of the genus Plasmodium that cause malaria namely: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malaria, and Plasmodium knowlesi. Plasmodium falciparum is the most common and virulent parasite. Plasmodium falciparum accounts for the majority of the burden of malaria in Sub-Sahara Africa. Plasmodium vivax accounts for half of the malaria burden in South and East Asia and > 80% of the malaria infection in America. The semisynthetic artemisinins are very potent and fast-acting antimalarials, inducing more rapid parasite clearance and fever resolution than any other currently used antimalarial drugs. They are particularly well suited for the treatment of severe Plasmodium falciparum. There are several artemisinins but the most effective artemisinin against Plasmodium parasites, including Plasmodium falciparum, is artemisinin-based combination which reduces selection pressure for the emergence of drug resistance. Artemisinin-based combination therapy has low toxicity and is considered safe for use in children and unlikely to be cause of fetal abnormality when is used in pregnancy. Children are more vulnerable than adults to Plasmodium parasites. The following malaria-endemic Sub-Sahara African countries Cambodia, Cameroon, Ghana, Kenya, Nigeria, Tanzania, and Zanzibar, which adopted antimalarial therapy with different artemisinins, switched to artemisinin-based combination as the first-line treatment against several Plasmodium parasites including Plasmodium falciparum. India switched to artemisinin-based combination as the first-line treatment against Plasmodium parasites. Artemisinins have been formulated for oral (dihydroartemisinin, artesunate, and artemether), intramuscularly (artesunate and artemether), intravenous (artesunate), and rectal (artesunate) routs. Bioavailability after oral dosing typically is ≤ 30%). Rectal administration of artesunate has emerged as an important administration route, especially in tropical countries where it can be lifesaving. Children with fever caused by malaria infection must be brought to the health service within 24 hours from the onset of fever. There is the need to carry out an international survey to establish the best artemisinin to act against Plasmodium parasites.

6- CONFLICT OF INTERESTS: None.

7- REFERENCES

1. Vinetz JM, Clain J, Bounkeua V, Eastman RT, Fidok D. Chemotherapy of Malaria. In the Goodman and Gilman's the Pharmacological Basis of Therapeutics. Twelfth Edition. Brunton LL, Chabner BA, Knollmann BC,

editors. Mc Graw Hill: New York; 2011. Pp. 1386-98.

2. Cullen KA, Mace KE, Arguin PM. Malaria Surveillance - United States, 2013. Centers for Disease Control and Prevention (CDC). MMWR Surveill Summ. 2016;65(2):1-22.

3. White NJ. Qinghaosu (artemisinin): the price of success. Science. 2008; 320(5874):330-4.

4. Eastman RT, Fidock DA. Artemisinin-based combination therapies: a vital tool in efforts to eliminate malaria. Nat Rev Microbiol. 2009; 7(12):864-74.

5. Medhi B, Patyar S, Rao RS, Byrav D S P, Prakash A. Pharmacokinetic and toxicological profile of artemisinin compounds: an update. Pharmacology. 2009; 84(6):323-32.

6. Bassi PU, Osakwe AI, Isah A, Suku C, Kalat M, Jalo I, et al. Safety of Artemisinin-Based Combination Therapies in Nigeria: A Cohort Event Monitoring Study. Drug Saf.2013; 36(9): 747-56.

7. Dellicour S, Hall S, Chandramohan D, Greenwood B. The safety of artemisinins during pregnancy: a pressing question. Malar J. 2007; 6:15.

8. Egunsola O, Oshikoya KA. Comparative safety of artemether-lumefantrine and other artemisinin-based combinations in children: a systematic review. Malar J. 2013; 12: 385.

9. Whegang SY, Tahar R, Foumane VN, Soula G, Gwét H, Thalabard JC, et al. Efficacy of non-artemisinin- and artemisinin-based combination therapies for uncomplicated falciparum malaria in Cameroon. Malar J. 2010; 9: 56.

10. Kakar Q, Sheikh S, Ahmed I, Khan MA, Jamil M, ElMohammady H, et al. Efficacy of artemisinin-based combination therapies for the treatment of falciparum malaria in Pakistan (2007-2015): In vivo response and dhfr and dhps mutations. Acta Trop. 2016; 164: 17-22.

11. Kamat VR, Nyato DJ. Community response to artemisinin-based combination therapy for childhood malaria: a case study from Dar es Salaam, Tanzania. Malar J. 2010; 9: 61.

12. Lawford H, Zurovac D, O'Reilly L, Hoibak S, Cowley A, Munga S, et al. Adherence to prescribed artemisinin-based combination therapy in Garissa and Bunyala districts, Kenya. Malar J. 2011; 10: 281.

13. Yeung S, Van Damme W, Socheat D, White NJ, Mills A. Access to artemisinin combination therapy for malaria in remote areas of Cambodia. Malar J. 2008; 7: 96.

14. Bennett A, Bisanzio D, Yukich JO, Mappin B, Fergus CA, Lynch M, et al. Population coverage of artemisinin-based combination treatment in children younger than 5 years with fever and Plasmodium falciparum infection in Africa, 2003-2015: a modelling study using data from national surveys. Lancet Glob Health. 2017; 5(4):e418-e427.

15. Praygod G, de Frey A, Eisenhut M. Artemisinin derivatives versus quinine in treating severe malaria in children: a systematic review. Malar J. 2008; 7: 210.

16. Khatib RA, Selemani M, Mrisho GA, Masanja IM, Amuri M, Njozi MH, et al. Access to artemisinin-based anti-malarial treatment and its related factors in rural Tanzania. Malar J. 2013; 12: 155.

17. Millar KR, McCutcheon J, Coakley EH, Brieger W, Ibrahim MA, Mohammed Z, et al. Patterns and predictors of malaria care-seeking, diagnostic testing, and artemisinin-based combination therapy for children under five with fever in Northern Nigeria: a cross-sectional study. Malar J. 2014; 13: 447.

18. Bhattarai A, Ali AS, Kachur SP, Mårtensson A, Abbas AK, Khatib R, et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. PLoS Med. 2007; 4(11):e309.

19. Shah NK, Tyagi P, Sharma SK. The impact of artemisinin combination therapy and long-lasting insecticidal nets on forest malaria incidence in tribal villages of India, 2006-2011. PLoS One. 2013; 8(2):e56740.

20. Kwarteng A, Asante KP, Abokyi L, Gyaase S, Febir LG, Mahama E, Konadu DG, Tawiah T, Adu-Gyasi D, Dosoo D, Amenga-Etego S, Ogutu B, Owusu-Agyei S. Provider compliance to artemisinin-based combination therapy at primary health care facilities in the middle belt of Ghana. Malar J. 2015; 14: 361.

21. Thiam S, Thwing J, Diallo I, Fall FB, Diouf MB, Perry R, et al. Scale-up of home-based management of malaria based on rapid diagnostic tests and artemisinin-based combination therapy in a resource-poor country: results in Senegal. Malar J. 2012; 11: 334.

22. Bruxvoort K, Kalolella A, Cairns M, Festo C, Kenani M, Lyaruu P, et al. Are Tanzanian patients attending public facilities or private retailers more likely to adhere to artemisinin-based combination therapy? Malar J. 2015; 14: 87.

23. Gomes M, Ribeiro I, Warsame M, Karunajeewa H, Petzold M. Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. BMC Infect Dis. 2008; 8: 39.

24. Singh N, Shukla MM, Chand G, Bharti PK, Singh MP, Shukla MK, et al. Epidemic of Plasmodium falciparum malaria in Central India, an area where chloroquine has been replaced by artemisinin-based combination therapy. Trans R Soc Trop Med Hyg. 2011; 105(3):133-9.

25. Onyango EO, Ayodo G, Watsierah CA, Were T, Okumu W, Anyona SB, et al. Factors associated with non-adherence to Artemisinin-based combination therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis. 2012; 12: 143.

26. Selemani M, Masanja IM, Kajungu D, Amuri M, Njozi M, Khatib RA, et al. Health worker factors associated with prescribing of artemisinin combination therapy for uncomplicated malaria in rural Tanzania. Malar J. 2013; 12: 334.

27. Huho BJ, Killeen GF, Ferguson HM, Tami A, Lengeler C, Charlwood JD, et al. Artemisinin-based combination therapy does not measurably reduce human infectiousness to vectors in a setting of intense malaria transmission. Malar J. 2012; 11: 118.

28. Thanh NV, Cowman AF, Hipgrave D, Kim TB, Phuc BQ, Cong LD, et al. Assessment of susceptibility of Plasmodium falciparum to chloroquine, quinine, mefloquine, sulfadoxine-pyrimethamine and artemisinin in southern Viet Nam. Trans R Soc Trop Med Hyg. 2001; 95(5):513-17.

29. Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, et al. Artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med. 2009; 361(5): 455-67.

30. Satimai W, Sudathip P, Vijaykadga S, Khamsiriwatchara A, Sawang S, Potithavoranan T, et al. Artemisinin resistance containment project in Thailand. II: Responses to mefloquine-artesunate combination therapy among falciparum malaria patients in provinces bordering Cambodia. Malar J. 2012; 11: 300.

31. Falq G, Van Den Bergh R, De Smet M, Etienne W, Nguon C, Rekol H, et al. Assessing the asymptomatic reservoir and dihydroartemisinin-piperaquine effectiveness in a low transmission setting threatened by artemisinin resistant Plasmodium falciparum. Malar J. 2016; 15(1): 446.

32. Bosman P, Stassijns J, Nackers F, Canier L, Kim N, Khim S, et al. Plasmodium prevalence and artemisinin-resistant falciparum malaria in Preah Vihear Province, Cambodia: a cross-sectional population-based study. Malar J. 2014; 13: 394.

33. Brown T, Smith LS, Oo EK, Shawng K, Lee TJ, Sullivan D, et al. Molecular surveillance for drug-resistant Plasmodium falciparum in clinical and subclinical populations from three border regions of Burma/Myanmar: cross-sectional data and asystematic review of resistance studies. Malar J. 2012; 11: 333.

34. Trape JF, Tall A, Diagne N, Ndiath O, Ly AB, Faye J, et al. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study. Lancet Infect Dis. 2011; 11(12):925-32.

35. Menard S, Morlais I, Tahar R, Sayang C, Mayengue PI, Iriart X, et al. Molecular monitoring of Plasmodium falciparum drug susceptibility at the time of the introduction of artemisinin-based combination therapy in Yaoundé, Cameroon: implications for the future. Malar J. 2012; 11: 113.