Artemisinin-based and non-Artemisinin-based combination therapies regimen for uncomplicated malaria in pregnancy and its impact on newborn and pregnancy outcomes in Mont Amba district, Kinshasa, Democratic Republic of the Congo

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ABBREVIATIONS

ACT	Artemisinin –based combination Therapy
ASAQ	Artesunate –Amodiaquine
AL	Artemether –Lumefantrine
ANC	Antenatal Care
DRC	Democratic Republic of the Congo
DHS	District Health Information
KOICA	Korea International Cooperation Agency
IUGR	Inta uterine growth retardation
LBW	Low birth weight
NMCP	National Malaria Control Programme
PMI	President Malaria Initiative
PCR	Polymerase Chain Reaction
PROM	Prelabor rupture of membranes
RDT	Diagnostic rapid test
SP	Sulfadoxine-Pyrimethamine
WHO	World Health Organization

ABSTRACT

During pregnancy, malaria infection in the mother can cause low birth weight and result in poor pregnancy outcomes. The choice of antimalarial drugs is critical in Democratic Republic of the Congo because of its malaria burden which is among the highest in sub-Saharan Africa. Artemisinin –based combination therapies regimen is recommended by World Health Organization for uncomplicated malaria in second or third trimester of pregnancy to treat uncomplicated malaria in pregnancy. However, the choice of drug to treat malaria during pregnancy depends on the prescriber knowledge, socioeconomic status, adherence and drugs availability in the health facility and all these may impact on pregnancy outcomes such as preterm delivery, stillbirth, abortion and newborn weight. This study aimed to examine the association between Artemisinin –based combination therapy regimen and low birth weight including pregnancy outcomes in Mont Amba district, Kinshasa.

It was based on patient records, cross-sectional, retrospective study in Mont Amba District, Kinshasa, from January to December 2018.The study population comprised pregnant mothers diagnosed with uncomplicated malaria in second or third trimester whom ages vary between 16 and 49. We used patient registries information about antimalarial drugs received, antenatal care visits, socioeconomic status, origin of those pregnant mothers and delivery information such as term, stillbirth, baby's weight, sex, from a secondary level health facility.

We sampled three hundred and sixty- four mothers and excluded all mothers aged below 16 or above 49, who did not deliver in the same health facility. Finally, two hundred and sixty-four mothers remained for our study. We categorized them in ACTs and non-ACTs groups according the antimalarial regimen they received. Continuous variables were calculated using two-sample Student's t-test. Categorical variables were analyzed using Chi-square or Fisher's exact test, as appropriate. Multivariate analysis was performed by logistic regression. All p-values were 2-tailed, with $p<0.05$ considered to be statistically significant. Statistical analyses were carried out by SPSS® version 25. Among 264 patients, there were 102(38.6%) using artemisinin –based combination therapies and 162(61.4%) using non- artemisinin –based combination therapies. Among these patients, 134(50.8%) were young women aged 20 to 29 years and majority of women came from Kisenso commune 215(81.4%). There were no significant differences in maternal age (28.3±6.4 vs. 27.7±6.3; p=0.782), outcome of pregnancy (term:72(70.6%) vs. 104(64.2%); p=0.283, preterm:28(27.5%) vs. 58(35.8%); p=0.159, stillbirth :2(2.0%) vs. 6(3.7%); p=0.715), infantile birth weight (3211.2g±504.0 vs. 3087.0±546); p=0.133, socioeconomic status (96(94.1%) vs. 160(98.8%); p=0.058), and antennal care (87(85.3%) vs 121(76.1%); p=0.072) between artemisinin –based combination therapies group and non- artemisinin –based combination therapies group. In the multivariate logistic regression, there was no significant difference in birth weight of infants born to women who received artemisinin –based combination therapies and those who did not (odds ratio, 1.208; 95% confidence

interval, 0.490-2.976; p=0.682). The current study results suggest that there is no impact of ACTs or non- ACTs treatment regimen on newborn weight preterm, abortion, and stillbirth

Keywords: Malaria, pregnancy, artemisisins, infant, low birth weight.

I. INTRODUCTION

A. Background

Malaria infection during pregnancy remains dangerous for mother and newborn and can lead to infant low birth weight, maternal anemia, miscarriage, and stillbirth. [Renee burger, Anna M. Van]. From the year 2006, the World Health Organization has recommended the use of Artemisinin-based combination therapy (ACT) for the treatment of uncomplicated *falciparum* malaria in the second and third trimester of pregnancy[1]. ACTs had been adopted as national policy for first-line treatment in 79 of 88 countries where Plasmodium *falciparum* is endemic by the year 2013[2] ; although, it has not always been clear whether this policy is also applicable to the treatment of pregnant women in the second and third trimester. In DRC and other countries where the policy has been adopted, many health workers continue to provide oral quinine, the drug recommended for treatment in the first trimester[3]. Over the past 2 decades, several studies have compared the efficacy and safety of ACTs to quinine and other non-ACTs in the second and third trimester[4], but individual studies often lack the power to draw definitive conclusions. Therefore, this study aimed to determine the association between ACTs regimen and low birth weight in DRC.

DRC is the second largest country by area in Africa (after Algeria) and the third most populated. A national census has not been conducted since 1984, but the Ministry of Health estimates the population to be 89,284,658 in 2017 and 91,873,913 in 2018, with the majority living in rural areas. The annual population growth rate is 3.2%. It shares borders with nine countries: Republic of Congo (Brazzaville), Central African Republic, Burundi,

South Sudan, Uganda, Rwanda, Tanzania, Zambia, and Angola, the last five of which are also PMI focus countries. The DRC sits on over 25 trillion dollars of minerals, which has the potential to significantly improve the economic situation of its residents, but this benefits only a small number of people and companies[5]. The country ranks 176 out of 188 countries in the world on the 2016 Human Development Index; an estimated 63% of the population lives on less than $1 per day. According to the 2013-14 Demographic and Health Survey (DHS), the under-five mortality rate is 104 per 1.000 live births, a substantial reduction from the previous rate of 158 per 1.000 (Multiple Indicator Cluster Survey 2010)[5].

There is still much to learn about the epidemiological stratification of malaria in the DRC, but generally the country can be divided into three epidemiological zones.

The mountainous zones of North Kivu are at an altitude of 1.000 to 1.500 meters. In this zone, malaria is hypo-endemic. The transmission season is very short and there can sometimes be no transmission for years. Malaria natural immunity is difficult to acquire, thus malaria occurs in the form of an epidemic and severe malaria affects all age groups.

In the tropical zone, transmission is seasonal and highest during the rainy season, which lasts five to eight months. Malaria mortality is also highest during the rainy season. Populations living in this zone are exposed to 60 to 400 infectious bites per person per year. Malaria natural acquired immunity starts building up around 10 years old, and severe malaria mostly affects younger and older children.

In the equatorial zone, transmission is intense and occurs year-round. People are exposed to up to 100 infectious bites per person per year and start building up natural immunity at an earlier age. Thirty to fifty percent of fevers in children under five years of age are due to malaria, and severe malaria is mainly observed in this age group.

It is estimated that 97% of the population lives in zones with stable malaria transmission lasting 8 to 12 months per year. The highest levels of transmission occur in zones situated in the north and west of the country. It is known throughout tropical Africa that the greatest burden of malaria morbidity and mortality falls on pregnant women and children under five years of age. In the DRC, malaria is linked with high mortality and morbidity, accounting for 39% of all outpatient visits and for 39% of deaths in 2014. Due to the fact that the majority of the population lives in high transmission zones, it has been estimated that the DRC accounts for 9% of all malaria cases and 10% of all malaria deaths in sub-Saharan Africa[5, 6].

The 2013-14 DHS, which constituted a representative sample for the eleven (11) old provinces, five (5) demonstrated that national malaria parasite prevalence in children 6-59 months to be between 23% and 34% depending upon the diagnostic test used: 22.7% for microscopy, 30.9% for RDTs, and 34.1% for polymerase chain reaction (PCR). However, the prevalence was found to be higher for those living in rural areas compared to urban; prevalence was highest in Orientale province and lowest in North Kivu (for all diagnostic methods). When comparing the PCR and microscopy results in the DHS supplemental malaria report shows that prevalence using PCR is approximately 50% higher

than with microscopy because it detects much lower levels of parasitemia; these findings are consistent with other studies. Molecular analyses suggest that mono-infection with Plasmodium *ovale* or Plasmodium *malariae* is rare (estimated at 0.6-1.7%). The survey also showed that 6.2% of Congolese children aged 6-59 months had severe anemia that could be associated with malaria (8.0 g/dl or less).

The National Malaria Control Strategic Plan for 2016-2020 divides the country into four strata based on parasite prevalence. The 2013-2014 DHS was conducted prior to the territorial reform that sub-divided the former 11 provinces into 26 new provinces. Provincial stratification based on malaria parasite prevalence, DRC-DHS II 2013-14 Strata Parasite Main Provinces % Population prevalence determinant I. ≤5% Mountain zone - hypo endemic Nord Kivu 8%[5].

There is still controversial opinion on the use of Artemisinin combination therapies (ACTs), the most efficacious antimalarial drugs available, are the recommended first-line treatment for Plasmodium *falciparum* malaria except in the first trimester of pregnancy[1, 7]. Preclinical studies have shown that artemisinin based combination therapies are embryotoxic and can induce fetal death and congenital anomalies at doses close to the therapeutic range in multiple animal species[8]. Artemisinin derivatives in rodents cause embryolethality as well as cardiovascular (ventricular septal and vessel defects) and skeletal defects[9]. Embryolethality was observed in monkey following prolonged treatment (12 to 20 d), but there were no malformations. The artemisinin embryotoxic effect occurs through depletion of embryonic erythroblasts[8]. It is unknown how findings from animal

studies would translate in humans because the mechanism of teratogenicity and the drug sensitive period may differ significantly in humans[10].

The last review by the World Health Organization (WHO) dates from 2006, when evidence on 170 human first-trimester artemisinin treatments was reassuring but insufficient to inform policy change[11]. That is why, quinine remains the recommended treatment for uncomplicated P. *falciparum* malaria in the first trimester. Presently, artemisinin derivatives are recommended in the first trimester only if quinine cannot be used or in cases of severe malaria where the benefit outweighs the potential risk.

It is estimated that each year over 30 million women become pregnant in malaria's prone areas in Africa, with most living in areas of stable malaria transmission[12]. Although the vast majority of women with malaria infections during pregnancy remain asymptomatic, infection increases the risk of maternal anemia and delivering a low-birth-weight (LBW) baby. LBW (2,500 g) is an important risk factor for infant mortality, and this review focuses on the impact of malaria during pregnancy on LBW and subsequent infant mortality in sub-Saharan Africa. There have been many papers describing the impact of malaria during pregnancy (and, more recently, attempts to quantify this burden (Steketee, R. W., B. L, 2001. The burden of malaria in pregnancy in malaria – endemic areas). However, there remains a poor understanding of the effects under different levels of transmission and in different gravidity groups. It is frequently reported that primigravidae and secundigravidae are the most at risk, and many of the literature on the burden of malaria during pregnancy have focused on women of these gravidities. However,

there is an increasing recognition that women of higher gravidities may also be at risk, particularly in areas of high transmission levels[13].

B. Objectives of the study

1. General objective

To determine the association between ACTs regimen and low birth weight in Mont Amba, Kinshasa, in DRC.

2. Specific objectives

1. To determine the impact of ACTs versus non-ACTs treatment on baby and pregnancy outcomes,
2. To recommend appropriate treatment regimen during pregnancy in Mont Amba District, Kinshasa, DRC.

II. LITERATURE REVIEW

1. Malaria in pregnancy situation in DRC

Recent Demographic and Health Survey (DHS) showed some evidence of improvement in the coverage of MIP interventions in the DRC. Use of ANC services remained relatively stable between the 2007 and 2013-14 DHS surveys, with 79% and 86% of women having at least two ANC visits, respectively. However, IPTp coverage only improved slightly over that same period, increasing from 5% in 2007 to 14% in 2013 for women receiving at least two doses of SP. Over the same period, use of bed nets among pregnant women increased substantially, from 7% in 2007 to 60% in 2013.

Last year PMI supported the implementation of MIP interventions in 178 health zones in 9 provinces. In the past 12 months, 492,174 treatments of SP were distributed to service delivery points. With FY 2018 funds, PMI will continue to supply ITNs and SP and to support training and supervision to ensure that providers are aware of and implementing the current guidelines regarding IPTp dosing and timing. SBCC activities will continue at both health facility and community levels and include counseling strategies on the use of ITNs during pregnancy, the importance of early attendance at ANC and obtaining SP at each visit after quickening, as well as correct diagnosis and treatment of malaria in pregnant women.

2. Case Management of malaria in DRC

Diagnosis and Treatment

The DRC National Malaria Control Strategic Plan states that by the end of 2020, 80% of fever cases should be tested for malaria, and 100% of those who test positive should receive appropriate treatment according to national guidelines. The national malaria case management guidelines and accompanying training package were revised and validated in April 2017 by the Disease Control Directorate. These updated guidelines largely conformed to WHO guidelines and standards, with the exception of age groups for pre-referral treatment with rectal articulate. For diagnosis, the guidelines state that all febrile patients should be tested for malaria by either microscopy or RDT. Microscopy is to be used at reference hospitals, primarily to monitor patients undergoing treatment for severe malaria and to monitor for treatment failure. RDTs are to be used in peripheral health centers and at the community level; they may also be used at reference hospitals as needed. The guidelines state that each provincial hospital and each general reference hospital should have a functioning laboratory to conduct microscopy. Currently, all 26 provincial hospitals have a functioning laboratory. For health zones, 393 of the 516 health zones have government-run (i.e., public) general reference hospitals and the remaining 123 health zones have either a faith-based hospital or a private health facility that serves as the reference hospital for the zone. In theory, all health zone general hospitals have at least one microscope, but current information about whether or not they are functional is not available, including in the PMI zones.

For uncomplicated malaria, the country supports two first-line ACT treatments: artesunate-amodiaquine (AS/AQ) and artemether-lumefantrine (AL). If one of the two first-line ACTs is not available or is poorly tolerated by the patient, the other can be used. In practice, AL tends to be primarily used in urban areas because patients have more options to obtain it from private pharmacies, while AS/AQ is used in rural areas. In case of confirmed treatment failure by microscopy to both first-line ACTs, the patient should be given dual therapy of quinine plus clindamycin. In case of a one-time epidemic, the national guidelines state that dihydroartemisinin-piperaquine (DP) could be used; for this reason, DP is included in the ongoing therapeutic efficacy study (details below).

For treatment of severe malaria, injectable articulate should be the first treatment option, followed by injectable artemether or IV quinine. At peripheral levels, including lower-level health facilities and community care sites, pre-referral treatment with rectal articulate is national policy, although roll out of training and commodities for pre-referral treatment is still underway. The national guidelines did not specify eligible age groups for rectal articulate (e.g., less than 6 years old per WHO guidelines) but do provided dosing guidelines for age groups of 6-13 years and 14 years and older in addition to children under 6 years old. With PMI support, the NMCP reviewed this guideline to align with the WHO, but decided to limit the use of rectal articulate to children under 5 years of age to line up with the information captured by current data collection tools and remain coherent with other strategic approaches that target this age group.

Care-seeking and treatment in the private sector (including non-profit and faith-based facilities, for-profit clinics, pharmacies, and drug shops) is widespread. According to the 2013-2014 DHS, among children with fever, 49% report seeking care in the public sector and 47% in the private sector. The non-profit/faith-based facilities often function much like the public-sector facilities in that they report into the routine health information system and abide by the national policies. But there are important differences in treatment availability in public and private outlets. A research project supported by ACT watch from 2013 to 2015 in Kinshasa and Katanga provinces included representative "outlet surveys" that assessed availability of malaria diagnostics and treatment at service delivery points, including public facilities and CHWs, private non-profit and for-profit facilities, regulated pharmacies, and unregulated drug shops and retailers. The last survey in 2015 found that drug shops represented 69% of outlets in Kinshasa and 59% in Katanga. In Kinshasa, 87% of public sector outlets stocked quality-assured ACTs; in Katanga 92% did. In the private sector, however, only 22% of private outlets stocked quality-assured ACTs in Kinshasa while 53% stocked them in Katanga.8 At the community level, integrated community case management (iCCM) is provided at community care sites (*sites de soin communautaire*). According to national guidelines, two volunteer community health workers (*relais communautaire*) are identified for each community care site. One CHW is responsible for providing diagnosis, treatment, and referral services while the other focuses on health promotion and community mobilization. CHWs are unpaid. Criteria for selection include a minimum level of education as well as having an established source of income, separate

from their unpaid health activities. Both CHWs are to be trained approximately every two to three years in malaria, pneumonia, and diarrhea diagnosis and treatment; this includes administration of RDTs, ACTs, and rectal articulate for severe cases. According to national guidelines, diagnosis with RDTs and malaria treatment is free for patients of all ages. Microscopy incurs a fee and other service provision fees may be applicable for malaria patients (e.g., consultation fees, paracetamol).

Antenatal care in DRC

It has been demonstrated that early and regular antenatal care attendance is strongly associated to better maternal and neonatal outcomes because pregnant women who do so fully benefit from its preventive and curative services. To reduce maternal and neonatal morbidity and mortality, the World Health Organization (WHO) recommended that pregnant women should receive ANC services at least 4 times starting from the first trimester of pregnancy. These provided services are used for prevention, early diagnosis, and treatment of pregnancy-related problems. In endemic malaria areas, some high-impact interventions such as the use of impregnated nets, the prompt management of malaria cases and anemia, and the intermittent preventive therapy (IPTp) are implemented to reduce malaria burden in pregnancy in areas with stable transmission of Plasmodium *falciparum*. Malaria is the most common parasitic disease in the world caused by Plasmodium and transmitted to humans by an infected female Anopheles mosquito. Through its National Malaria Control Program, the DRC is committed to achieve by 2015 the prevention of 80% of pregnant women. Intermittent preventive therapy (IPTp) is one of the preventive services

recommended by the WHO to control this disease. But for this IPTp to be effective it must be administered according to standards that are based, on one side, on its early onset before 20 weeks and, on the other, on the number of recommended doses to be administered. The study undertaken by Célestin Ndosimao Nsibu, et all., in 2016 showed that than 22% of Congolese pregnant women attend the ANC facilities in the first trimester as reported in 2010 from the MICS survey and therefore most of the targeted women do not benefit from all delivered high-impact interventions. Present recommendations of the WHO impose 4 doses of IPTp to women during their pregnancy[14].

Antimaalarial and traditional plants used in DRC

Malaria is the most prevalent parasitic disease and the foremost cause of morbidity and mortality in the DRC. For the management of this disease, large Congolese population recourses to traditional medicinal plants. To date the efficacy and safety of many of these plants have been validated scientifically in rodent malaria models. In order to generate scientific evidence of traditional remedies used in the DRC for the management of malaria, and show the potential of Congolese plants as a major source of antimalarial drugs, Patrick B. Memvanga a, n et all., in 2015 worked on the antiplasmodial and toxicological properties of the Congolese antimalarial plants investigated during the period of 1999–2014. In doing so, a useful resource for further complementary investigations is presented. It has been proven that approximately 120 extracts and fractions obtained from Congolese medicinal plants showed pronounced or good antiplasmodial activity. A number of compounds with interesting antiplasmodial properties were also isolated and identified. Some of these

compounds constituted new scaffolds for the synthesis of promising antimalarial drugs. Interestingly, most of these extracts and compounds possessed high selective activity against Plasmodium parasites compared to mammalian cells. The efficacy and safety of several plant-derived products was confirmed in mice, and a good correlation was observed between in vitro and in vivo antimalarial activity. The formulation of several plant-derived products also led to some clinical trials and license of three plant-derived drugs (Manalarias, Nsansiphoss, and Quinine Pharmakinas) which are among antimalarial plant drugs used during this current study. Antimalarial plants utilized in Congolese traditional medicine represent an important source for the discovery and development of new antimalarial agents. However, in order to ensure the integration of a larger number of plant-derived products in the Congolese healthcare system, some parameters and trends should be considered in further researches, in agreement with the objectives of the "Traditional Medicine Strategy" proposed by the World Health Organization in 2013. Among them, we have: evaluation of geographical and seasonal variation, investigation of reproductive biology, assessment of prophylactic antimalarial activity, evaluation of natural products as adjuvant antioxidant therapy for malaria, development of plant-based combination therapies and monitoring of herbal medicines in pharmacovigilance systems[15].

I. MATERIAL AND METHODS

It was a patient records based, cross-sectional, retrospective study in Mont Amba District, Kinshasa, from January to December 2018.The study population comprised pregnant mothers diagnosed with uncomplicated malaria in second or third trimester whom ages vary between 16 and 49. We used patient registries information about antimalarial drugs received, antenatal care visits, socioeconomic status, origin of those pregnant mothers and delivery information such as term, stillbirth, baby's weight, sex, length from January until December 2018 from a secondary level health facility.

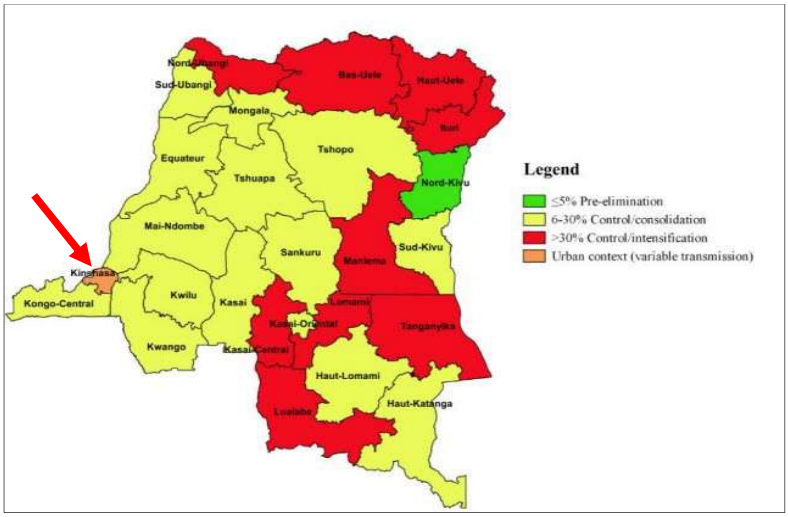


Figure 1: Study location general view of the capital city of DRC: Kinshasa[16](Source: African Financial and Economic Data)

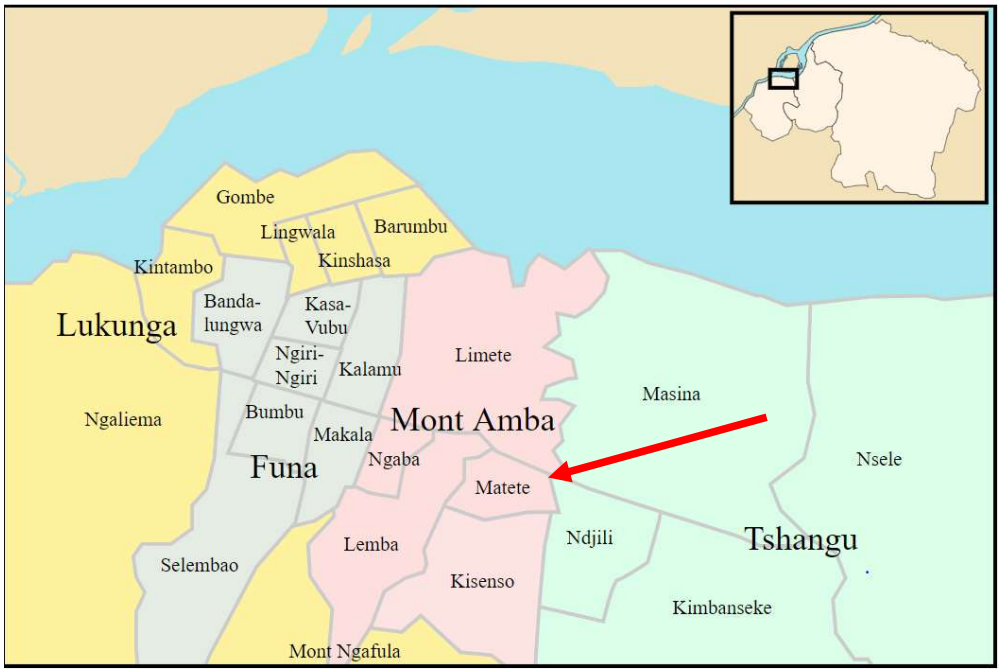


Figure 2: Specific location of study site: Mont Amba District (Matete, Lemba, Limete, Kisenso, N'djili, Masina)[17]

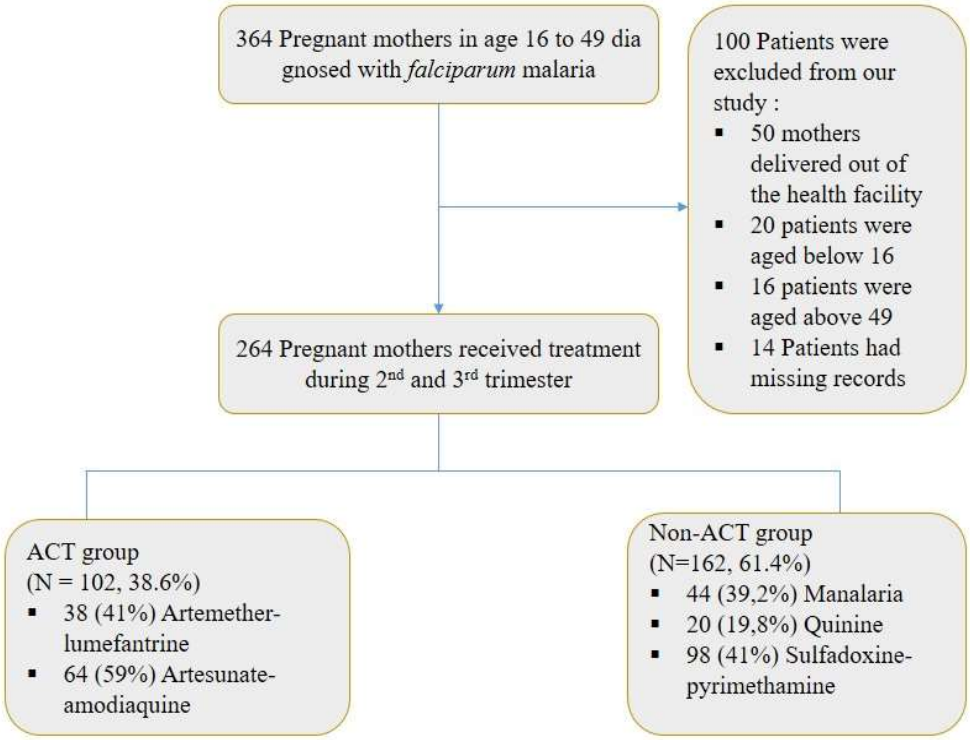
We sampled three hundred and sixty- four mothers and excluded all mothers aged below 16 or above 49, who did not deliver in the same health facility. Finally, two hundred and sixty-four mothers remained for our study. We categorized them in ACTs and non-ACTs groups according the antimalarial regimen they received. Continuous variables were calculated using two-sample student's t-test. Categorical variables were analyzed using Chi-square or Fisher's exact test, as appropriate. Multivariate analysis was performed by

logistic regression. All p-values were 2-tailed, with $p<0.05$ considered to be statistically significant. Statistical analyses were carried out by SPSS® version 25.

Table 1. Different antimalarial treatments received by pregnant mothers

Abbreviation	**Molecules**	**Firm denominations**
AS/AQ	Artesunate -Amodiaquine	ACT tablets
AL	Artemether-Lumefantrine	Combiart® Tablets
SP	Sulfadoxine-pyrimethamine	Fansidar® Tablets
QUININE (Pharmakinas)	Quinine sulfate	Quinine® Tablets
Traditional plant	Traditional plant	Manalaria® Tablets

Figure 3**: Study flowchart**



IV. RESULTS

A. General characteristics

Among 264 patients, there were 102(38.6%) using ACT and 162(61.4%) using non-ACT. Among these patients, 134(50.8%) were young women aged 20 to 29 years and the majority of women came from Kisenso commune 215(81.4%) as shown in Table 2.

Table 2. General characteristics

Characteristics	Numbers (n=264)	Percentage
Age		
<20 years	28	10.6
20-29	134	50.8
30-39	93	35.2
40-49	9	3.4
Parity		
1	121	45.8
2	66	25.0
3 and above	77	29.2
Origin		
Kisenso	215	81.4
Lemba	6	2.3
Limete	2	0.8
Masina	1	0.4
Matete	39	14.8
N'djili	1	0.4
ANC		
No	53	20.3
Yes	208	79.7
Treatment		
Non ACT	162	61.4
ACT	102	38.6
Birth weight		
≤2500g	24	9.6
>2500g	227	90.4
Newborn sex		
Female	141	55.5
Male	113	45.5
Outcome		
Term	178	67.4
Preterm	86	32.6

* ANC: Antenatal Care
*ACTs: Artemisin-based combination therapy
*Non ACTs: Non Artemisinin based combination therapy

B. Comparison of clinical characteristics between ACT and Non-ACT groups

There were no significant differences in maternal age (28.3±6.4 vs. 27.7±6.3; p=0.782), outcome of pregnancy (term:72(70.6%) vs. 104(64.2%); p=0.283, preterm:28(27.5%) vs. 58(35.8%); p=0.159, stillbirth:2(2.0%) vs. 6(3.7%); p=0.715), infantile birth weight (3211.2g±504.0 vs. 3087.0±546.1), socioeconomic status (96(94.1%) vs. 160(98.8%); p=0.058), and antennal care (87(85.3%) vs 121(76.1%); p=0.072) between ACT group and non-ACT group as shown in Table 3.

Table 3. Comparisons of clinical characteristics between ACT group and Non-ACT group.

Characteristics	**ACT group (N =102)**	**Non-ACT group (N = 162)**	***p***
Age (years)	28.3±6.4	27.7±6.3	0.782
Outcome of pregnancy			
Term	72(70.6)	104(64.2)	0.283
Preterm	28(27.5)	58(35.8)	0.159
Abortion	1(1.0)	4(2.5)	0.652
Stillbirth	2(2.0)	6(3.7)	0.715

Continuous variables are shown as means ± standard deviation and medians ± IQR (3^{rd} interquartile range-1^{st} interquartile range) and categorical variables as numbers (percentage). MIC; Minimum inhibitory concentration

C. ACT effect for malaria in pregnancy; Multivariable analysis

In the multivariate logistic regression, there was no significant difference in birth weight of infants born to women who received ACT and those who did not (odds ratio, 1.208; 95% confidence interval, 0.490-2.976; p=0.682).

Table 4. ACT effects of malaria in pregnancy; Multivariable analysis

Variables	**Odds ratio**	**95% confidential interval**	***p***
Age (years)	1.014	0.974-1.056	0.493
Preterm	0.706	0.395-1.262	0.240
Abortion	0.578	0.060-5.533	0.634
Stillbirth	0.654	0.124-3.457	0.617

IV. DISCUSSION

In this study, we accessed the impact of ACTs on the birth weight of newborns and pregnancy outcomes from mothers who suffered from uncomplicated P. *falciparum* malaria during pregnancy in second or third trimester in Mont Amba, in one of highest transmission malarial areas in the capital city of Kinshasa. Based on collected data, we aimed to evaluate ACTs regimen treatment by itself if it has considerable consequences or not on the newborn weight and pregnancy outcomes. And among the non-ACT treatments, we had Quinine and traditional plant (Manalaria®) which is not also recommended in the national malaria control guideline for the treatment of uncomplicated malaria in DRC during all trimesters of pregnancy, however well tolerated and cost effective for most of pregnant women with low socio-economic status. This study suggests that there was no statistically significance difference among the group of mothers treated with ACTs and Non- ACTs, this means that non-ACTs may impact positively pregnancy outcomes and baby's birth in Mont Amba district, being given that it showed no difference on birth weight and pregnancy outcomes. These findings are surprising on the fact that those non-ACTs molecules are not suggested by malaria control national guidelines. we may suggest the use of non-ACTs as alternative to treat uncomplicated malaria in Kinshasa as another option for pregnant women with low socioeconomic status we cannot afford ACTs in terms of price and contribute to improved access to antimalarial drugs to many mothers during the pregnancy. These current results correlate with the study conducted by Kangulu et al., (2014) in semi-rural Kamina in DRC which concluded that they are many factors that contribute to low birth weight such as

socio-economic status, age less than 18 years and upper than 35 years, ANC, parity and prematurity, twin pregnancy and newborn gender (female) are factors that determine birth weight., not antimalarial drugs by its self[18].

Similarly, findings of this study also correlate with Tshotethi, et al, 2019 in South Africa which showed that the main reason for LBW is preterm delivery, but the etiology of preterm delivery remains unknown[19]. Most authors agree that preterm delivery can be caused by medical conditions, and infections like hypertension, malaria, syphilis, and HIV infection. A systematic review focusing on developing countries, found a strong association between maternal HIV infection and LBW. Contrastingly, a randomized control trial (RCT) study in Malawi, failed to find an association between HIV and LBW, even though the prevalence of HIV was 26.2%. Therefore, there is conflicting evidence on the relationship between HIV infection and LBW. Broek *et al*, 2014 found that maternal anemia was another risk factor for LBW (72.6% versus 64.5% in term pregnancy)[20]. A multinational RCT conducted in sub-Saharan Africa did not find any association between maternal anemia and LBW, but maternal age of younger than 19 years and being malnourished were associated with LBW. Kumar *et al*, 2010 compared adverse birth outcomes between anemic and non-anemic mothers, and found that maternal hemoglobin status was an importance predictor of neonate weight and length. One might argue that malnutrition, rather than just anemia, in low-income countries, may affect the weight of neonates. Maternal nutrition affects the growth of the baby in utero and the eventual birth weight. Maternal infection may also limit the growth of the baby[21].

In sub-Saharan Africa, maternal malaria infection is an important predictor of adverse birth outcomes, including LBW or premature birth. In Congo, 94.5% of LBW babies were born to mothers who had malaria. In Malawi, which is a malaria endemic area; a RCT showed that 36.4% women who had malaria delivered premature babies, compared to 28.5% women who did not have malaria. Other causes that have been reported by different authors are non-communicable diseases such as hypertension or diabetes. Ngoma *et al,* 2016 found that teenage mothers had a higher risk of delivering a LBW infant than adult mothers (16% versus 9%)[22]. In contrast, Hoque et. Al, 2008 compared the incidence of adverse obstetric and perinatal outcomes of adult mothers to teenage mothers. They found that slightly more teenage mothers (14.3%) than adult mothers (13.7%) gave birth to LBW babies (P = 0.56)[23]. Further binary logistic regression showed that teenage pregnancy did not predict a LBW outcome. Similarly, in a Pretoria Tertiary Hospital, teenage mothers had 17.2% LBW babies compared to 12.6% of adult mothers (P = 0.140) and age did not predict LBW.

Moreover, the findings of this study correlated also with Tshotetsi et all in 2019 which suggested that Women who attended fewer than five ANC visits were predisposed to give birth to low birth weight babies[19]. Mothers should be encouraged to attend ANC visits to detect adverse events like premature rupture of membranes and premature labor to avoid low birth weight. Sociodemographic factors associated with LBW were maternal age, race of the mother and the residence of the mother. Women older than 20 years (n = 412, 38.54% of all LBW deliveries) were at risk of LBW delivery (Odds ratio [OR] 1.33, CI

1.00 to 1.77). Prenatal factors associated with LBW were ANC attendance, the number of ANC visits, not having a syphilis test and a positive HIV status. Almost five percent (4.80%) of mothers who did not attend ANC delivered a LBW infant. Mothers who did not attend ANC had increased risk (OR 2.65, CI 1.58 to 4.43) of delivering a LBW baby compared to those who attended ANC. Women who did not attend ANC, or had missing information on the ANC visits had increased risk of delivering a LBW infant (OR 3.76, CI 2.27 to 6.22) compared to women who attended more than 5 ANC visits. Women who attended ANC 1 to 4 times, had an increased risk (OR 1.72 CI 1.22 to 2.43) of delivering LBW babies compared to women who attended more than 5 times. Obstetric risk factors associated with LBW included women with preeclampsia (OR 3.74, CI 1.04 to 8.84) and premature rupture of membranes (PROM) (OR 6.74, CI 2.27 to 20.02). Anaemia, hypertension and infections were not significant predictors of LBW deliveries. In adjusted analysis, maternal age was associated with LBW (adjusted odds ratio [AOR] 12.20, CI 3.90 to 38.02) for older women compared to younger women. Women who had fewer than 5 ANC visits also remained significantly associated with LBW (AOR 1.30, CI 1.06 to 1.61) compared to those who attended 5 or more visits. Additionally, PROM remained significantly associated with LBW (OR 7.33, CI 2.43 to 22.12). Preterm delivery also remained associated with LBW (OR 7.15, CI 5.18 to 9.89) and male infants remained less likely to be LBW (OR 0.52, CI 0.52 to 0.92).

Study limitations

This study had several limitations that need to be taken into consideration. As we used data from cross-sectional surveys, our study reported only the association, however, it did not make a causal relationship. The study period was short to permit us having strong conclusions to be generalized.

Secondly, we had time constraints, which did not allow us to have a big data sample from many years back.

Finally, we did not have the possibility to get access to the treatments received by those mothers during their pregnancy so as to have an idea on which diseases they suffered from, excluding malaria that could have an impact on babies' weight. And also, we did not have information on parent's genetic morphology or body features such as height, size, nutritional status that could impact also on their baby's weight.

V. CONCLUSION

At the end of this study which allowed us to establish the impact of ACTs and non-ACTs on newborn weight from mothers who contracted *falciparum* uncomplicated malaria and their pregnancy outcomes in Mont Amba district, in DRC, it has been demonstrated that ACTs regimen by itself could not explain LBW, abortion, preterm and stillbirth from women who delivered after having suffered from malaria in second or third trimester , however , there are many other factors or variables to consider such as age of the mother , socioeconomic status , parity , type of pregnancy (twin pregnancy) , number of ANC followed , infections contracted during the pregnancy , genetic features of parents can probably explain our study findings . The current study results suggest that there is no impact of ACTs or non- ACTs treatment regimen on newborn weight, preterm, abortion, and stillbirth.

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