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FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES

REPUBLIQUE DU CAMEROUN
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UNIVERSITÉ DE YAOUNDÉ I
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FACULTE DE MEDECINE ET DES SCIENCES BIOMEDICALES

PARASITOLOGICAL AND OBSTETRICAL OUTCOME OF SULFADOXINE-PYRIMETHAMINE IN THE INTERMITTENT PRESUMPTIVE TREATMENT OF MALARIA IN PREGNANCY

Research Thesis to obtain an MD

Presented and defended by:

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ACADEMIC YEAR 2023-2024

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LIST OF ABBREVIATIONS

MiP…….malaria in pregnancy

p.falciparium……..plasmodium falciparum

WHO……world health organization

LBW…….low birth weight

IPTp……intermittent preventive treatment of malaria in pregnancy

ITNs……..insecticide treated nets

SP…….sulphadoxine-pyrimethamine

ANC……antenatal care

Pfdhr……p.falciparum dihydrofolate reductase

Pfdhps……p.falciparum dihydropterate synthetasE

RBC……red blood cell

IEs……..infected erythrocytes

CSA…….chondrontine sulphate A

ICAM……intracellular adhesion molecule

VSAPAM……variant surface antigen pregnancy associated malaria

VAR2CSA…….. variant surface antigen

PFEMP…….p.falciparum erythrocyte membrane protein

IRS…….Indoor Residual Sray

Th1……T helper 1

Th2…… T helper 2

TNF…….. Tumor necrotic factor

INF…….interferon

IUGR…….Intrauterine growth retardation

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DEDICATION

I DEDICATE THIS WORK TO MY BELOVED MOTHER MOTANGA CAROLINE, MY FATHER ESAMBI LAZARUS AND OTHER FAMILY MEMEBERS FOR THEIR UNCONDITIONAL LOVE AND UNWAVERING SUPPORT.

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- **HD**= Head of Department
- **P**= Professor
- **AP**= Associate Professor
- **SL**= Senior Lecturer
- **L**= Lecturer

PHYSICIAN OATH

Declaration of Geneva adopted by the World Medical Association amended at the 68th General assembly in Chicago in October 2017

As a member of the medical profession:

I solemnly pledge to dedicate my life to the service of humanity;

The health and well-being of my patient will be my first consideration;

I will respect the autonomy and dignity of my patients;

I will maintain the utmost respect for human life;

I will not permit consideration of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient;

I will respect the secrets that are confided in me, even after the patient has died;

I will practice my profession with conscience and dignity and in accordance with good medical practice;

I will foster the honor and noble traditions of the medical profession;

I will give to my teachers, colleagues and students the respect and gratitude advancement of health care;

I will attend to my own health, well-being and abilities in order to provide care of the highest standard;

I will not use my medical knowledge to violate human rights and

ABSTRACT

INTRODUCTION: Given how susceptible pregnant women are to contracting malaria and the associated materno-fetal complications, they were prophylactically treated with a combination of sulfadoxine and pyrimethamine. However, few studies have been carried out on the obstetrical and parasitological effects of this medication in the Jean Zoa Medical Center. This study was thus intended to shed more light on the possible obstetrical and parasitological outcomes.

METHODOLOGY: Consenting pregnant women were enrolled and a prospective efficacy study carried out, after administration of three doses of sulfadoxine-pyrimethamine to pregnant women from Yaoundé not presenting with symptoms and signs of malaria infection and negative parasitemia. We then followed up these women for three months during which slides were prepared on follow-up days 7, 14, 28, 42, 56, 70 and 84. Those with positive slides were removed from the study and those with negative slides were given additional doses of sulfadoxine-pyrimethamine and followed up as above.

RESULTS: Our sample size was 123 women, with an average age of 28.4, majority of whom were single and business women. Most(56.1%) were multigravidae and 78.9% were in the second trimester. The majority, that is; 77.24% received IPTp-SP, out of which 39% received more than 3 doses. We had 30 positive microscopies throughout the study. There was a statistically significant relationship between age(p=0.023), gravidae(p=0.029), IPTp-SP (0.00005) and marital status. The cumulative failure rate of this study was 13.9%.

CONCLUSION: At the end of this study, we concluded that the use of IPTp based on SP is associated with lower rate of malaria, was effective in preventing malaria in 75.6% of pregnant women and no adverse outcome was associated with the use of Sulfadoxine-Pyrimethamine for Intermittent preventive treatment as observed in the study population

RECOMMENDATIONS: The ministry of public health should organize training sessions to create awareness on IPTp, ensure a constant supply of SP to health facilities. Researchers should carry out a similar study on a larger population size and extend follow up to post-partum period and to pregnant women to start their antenatals as early as possible

Keywords: outcome, efficacy, Intermittent preventive treatment and pregnant women

RÉSUMÉ

INTRODUCTION : Compte tenu de la vulnérabilité des femmes enceintes au paludisme et des complications materno-fœtales associées, elles ont été traitées prophylactiquement par une association de sulfadoxine et de pyriméthamine. Cependant, peu d'études ont été réalisées sur les effets obstétricaux et parasitologiques de ce médicament au Centre Médical Jean Zoa. Cette étude avait donc pour objectif d'apporter plus de lumière sur les possibles issues obstétricales et parasitologiques.

MÉTHODOLOGIE : Des femmes enceintes consentantes ont été recrutées et une étude prospective d'efficacité a été réalisée, après administration de trois doses de sulfadoxine-pyriméthamine à des femmes enceintes de Yaoundé ne présentant pas de symptômes et de signes d'infection palustre et de parasitémie négative. Nous avons ensuite suivi ces femmes pendant trois mois au cours desquels des lames ont été préparées les jours de suivi 7, 14, 28, 42, 56, 70 et 84. Celles dont les lames étaient positives ont été retirées de l'étude et celles dont les lames étaient négatives ont reçu des doses supplémentaires de sulfadoxine-pyriméthamine et ont été suivies comme ci-dessus.

RÉSULTATS : Notre échantillon était de 123 femmes, d'un âge moyen de 28,4 ans, dont la majorité étaient des femmes célibataires et des femmes d'affaires. La plupart (56,1 %) étaient multipares et 78,9 % étaient au deuxième trimestre. La majorité, soit 77,24 %, a reçu l'IPTp-SP, dont 39 % ont reçu plus de 3 doses. Nous avons eu 30 microscopies positives tout au long de l'étude. Il y avait une relation statistiquement significative entre l'âge ($p = 0,023$), la paresseuse ($p = 0,029$), l'IPTp-SP (0,00005) et l'état matrimonial. Le taux d'échec cumulé de cette étude était de 13,9 %.

CONCLUSION : À la fin de cette étude, nous avons conclu que l'utilisation du TPIg basé sur la SP est associée à un taux plus faible de paludisme, qu'elle est efficace pour prévenir le paludisme chez 75,6 % des femmes enceintes et qu'aucun effet indésirable n'est associé à l'utilisation de la sulfadoxine-pyriméthamine pour le traitement préventif intermittent comme observé dans la population étudiée.

RECOMMANDATIONS : Le ministère de la santé publique devrait organiser des sessions de formation pour sensibiliser au TPIg, assurer un approvisionnement constant en SP dans les établissements de santé. Les chercheurs devraient mener une étude similaire sur une population plus large et étendre le suivi à la période post-partum et aux femmes enceintes pour commencer leurs soins prénatals le plus tôt possible.

Mots clés : Résultats, efficacité, traitement préventif intermittent et femmes enceintes

CHAPTER I: INTRODUCTION

1. BACKGROUND

Malaria in pregnancy (MiP), with P. falciparum accounting for over 99% of cases, is a major public health problem, with substantial risks for the mother, her fetus and the newborn, especially in sub-Saharan Africa.[1] In 2020, in 33 moderate to high malaria transmission countries in the World Health Organization (WHO) African region, there were an estimated 33.8 million pregnancies, 34% of which were exposed to the malaria infection. West Africa had the highest prevalence of exposure to malaria during pregnancy at 39.8%, followed by central Africa with 39.4% then 22% in the East and Southern parts of Africa. Still this same year it was estimated that malaria infection in pregnancy in these 33 countries resulted in 819 000 neonates with low birthweight(LBW), with 54.1% of these children being in the sub region of West Africa.[2]

In Cameroon, just as in other endemic areas, malaria in pregnancy has been shown to be a cause of maternal anemia, intra-uterine growth retardation, low birth weight, stillbirths and abortions. Pregnant women are more likely to become infected, with infected rate being higher in primigravidae than multigravidae women.[3]

WHO-recommended malaria prevention tools and strategies include; effective vector control, the use of preventive antimalarial drugs and vaccine. Vector control is a vital component of malaria control and elimination strategy as it is highly effective in preventing infection and reducing disease transmission. The 2 core interventions are insecticide-treated nets (ITNs) and indoor-residual spraying (IRS). Preventive chemotherapy is the use of medicines, either alone or in combination, to prevent malaria infections and their consequences. It requires giving a full treatment course to vulnerable population (generally infants, children under 5 years of age and pregnant women) at a designated time points during the period of greatest malaria risk, regardless of whether the recipients are infected with malaria. Preventive chemotherapy includes perennial malaria chemoprevention (PMC), seasonal malaria chemoprevention (SMC), intermittent preventive treatment of malaria in pregnancy (IPTp) and school-aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration. Since October 2021, WHO also recommends broad use of the RTSS/AS01 malaria vaccine among children living in regions with moderate to high P. falciparum malaria transmission.

The WHO recommends a three-pronged approach to MiP in areas with moderate to high transmission rates; Intermittent Preventive Treatment of malaria in pregnancy (IPTp),

Insecticide Treated Nets (ITNs) and effective and prompt management of clinical malaria. These approaches are commonly delivered through collaboration between malaria and reproductive health programs.[4]

In most African countries, sulfadoxine-pyrimethamine (SP) remains the recommended drug for IPTp. Based on findings of multi-center trials on the evaluation of IPTp-SP, three or more doses of IPTp-SP were associated with less placental malaria, higher mean birthweight and fewer low birth weight compared with two doses previously used. As a result, WHO policy on IPTp-SP was revised and recommends uptake of at least three SP doses with each dose administered at each scheduled antenatal care(ANC) visit, at least 1 month apart starting from the beginning of the second trimester until delivery.[5] In 2016, WHO recommended the administration of SP every month starting from the 13^{th} week of gestation. It has been shown that the usage rate of IPTp-SP in some towns in the south West Region of Cameroon was 88.7% which was above the 80% set by Roll Black malaria in pregnancy for 2010, but less than the ambitious 100 % coverage set in 2015 by the same organization. It was also shown that the lone independent factor associated to IPTp-SP use was the number of antenatal care (ANC) attended, which is similar to the finding made in Sudan though different from those obtained in a study in Tanzania where the number of ANCs had no effect on IPTp-SP use. Other factors associated with IPTp-SP use were age, occupation, education level and the trimester of pregnancy.[3]

Effectiveness of IPTp-SP is threatened by rising levels of parasite resistance to SP in several countries across Africa. Emergence and successive acquisition of polymorphisms in both the p. falciparum dihydrofolate reductase/dihydropteroate synthetase (pfdhfr/pfdhps) genes are associated with a high-level of SP resistance and clinical treatment failure in several epidemiological settings. Parasites harboring the K540E mutation, which is a proxy for the pfdhfr–pfdhps quintuple mutant is strongly linked with resistance rendering SP ineffective to clear P. falciparum infections. Sextuple mutant parasites (quintuple mutant plus the additional pfdhps A581G mutation) defined as super-resistant parasites have been associated with a loss of IPTp-SP efficacy. This resistance rendered SP ineffective to clear P. falciparum infection. In Yaoundé, Cameroon, highly resistant parasites to SP have been isolated from pregnant women with symptomatic p. falciparum infection. Also, a high prevalence of p. falciparum resistance parasites among pregnant and non-pregnant women has been reported along the slope of mount Cameroon. In Cameroon, the wide spread of SP resistance may undermine antimalarial policies. However, IPTp-SP still has beneficial outcomes in reducing the odds of

low birthweight, increasing infant birthweight and maternal hemoglobin levels. No additional benefits were observed by adding a third dose of SP compared to the standard 2-dose regimen, this is contrary to the meta-analysis that led to WHO to recommend three or more doses of IPTp. This suggest that SP is potentially failing in West Africa.[5]

Thus, continuous monitoring and evaluation of the obstetrical outcomes of SP in Cameroon is crucial. Hence, this study will determine the obstetrical outcomes of IPTp.

2. STATEMENT OF RESEARCH PROBLEM

Since the emergence of P falciparum resistance to malaria drugs in Cameroon, concerns have been raised about the safety and outcomes of SP use for the prevention and treatment of asymptomatic malaria in pregnancy in high to moderate transmission areas. WHO malaria report estimated that about 34% of pregnant women were exposed to malaria infection in 2021.[2]

In the face of these number of women exposed to malaria in pregnancies and the emergence of SP resistance in malaria in the WHO African region countries with Cameroon included, there must therefore be a continuous monitoring of the effectiveness of IPTP-SP in this Region. We therefore carried out this study to monitor the effectiveness of IPTp-SP.

a. Justification and rational of the research topic

Malaria in pregnancy is dangerous to both the fetus and mother. Any intervention to prevent malaria must be safe and effective so as to ensure adequate obstetrical outcomes while also safeguarding the well-being of pregnant women.

Studies to map the parasitemia and obstetrical outcomes of IPTp-SP are thus essential for planning containment and elimination strategies of malaria in pregnancy in Cameroon.

b. Research Question

What are the parasitological and obstetrical outcomes of using SP for IPT in pregnancy?

CHAPTER II: AIMS AND OBJECTIVES

1. AIM

This study has as primary aim to evaluate the efficacy and safety of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine.

1.1. General objective

Our main objective was to determine the parasitological efficacy and obstetric outcome of IPTp-SP.

1.2. Specific objectives

1. Describe the socio-demographic and obstetric characteristics of the participants.
2. Show the prevalence of p. falciparum malaria in pregnancy.
3. Describe the efficacy of SP in preventing parasitemia during pregnancy.
4. Describe the obstetrical outcome of SP during pregnancy

CHAPTER III: LITERATURE REVIEW

1. DEFINITION

Malaria is an acute parasitic disease of the tropics and sub-tropics, caused usually by the invasion and destruction of the red blood cells by one or more of the five species of the genius plasmodium. Human malaria is caused by five different species of plasmodium: P falciparum, P vivax, P ovale, P knowlesi and P malariae. Malaria is transmitted to humans through the bite of female *Anopheles* mosquitoes. *Anopheles* mosquitoes feed on blood for survival and production of eggs. During feeding, infected female *Anopheles* mosquito inoculates the infective sporozoites from its salivary gland into human circulation. After inoculation, parasites circulate with blood and those reaching to the liver undergo one cycle development. Then, parasites infect and multiply inside red blood cells to bring the characteristic signs and symptoms.[6] The clinical manifestations include fever, joint pain, chills, headache and vomiting which usually appear between 10 and 15 days after the *Anopheles* mosquito bite. In addition, malaria may also be transmitted through blood transfusion and congenitally.[7] Malaria in pregnancy is a major cause of maternal death, maternal anemia and adverse obstetric outcomes (spontaneous abortion, preterm delivery, growth restriction/low birth weight, stillbirth, congenital infection, neonatal mobility) in geographic areas where malaria infections occur commonly in pregnant women. Clinical manifestation varies according to the infecting species, and according to the genetics, immune status , age of the infected person, parity.[6]

2. EPIDEMIOLOGY AND BURDEN OF MALARIA IN PREGNANCY

Malaria affects nearly half the world's population (CDC,2021). Globally, 241 million cases of malaria were reported in 2020 with 627,000 people dying and the majority of them were children in Africa (WHO,2022). The African region carries a disproportionately high share of the global malaria burden (world bank 2022).

In 2015, sub-Sahara Africa accounted for 90% of malaria cases and 92% of malaria deaths (AHO, 2022). Approximately 35 million pregnant women in Sub-Saharan Africa are at risk of contracting malaria each year and at least 25% of pregnant women are predicted to have the disease each year (wagbatsoma & omoike,2008).[8] There is a wealth of evidence that shows that the risk of malaria is higher in pregnant than their non-pregnant counterparts possibly due to immunological, hormonal changes or by the higher attractiveness of pregnant women to mosquitoes.[9] In geographical areas with high transmission of malaria, such as sub-Saharan

Africa, the risk of Plasmodium falciparum infection increases when women get pregnant, with potential adverse consequences for mother and child. Malaria prevalence is highest in the first and second trimester of pregnancy,[10] and the risk might not immediately return to pre-pregnancy levels after delivery.[11] In these geographical areas with high transmission, defined as parasite prevalence of 10% or more in children aged 2–9 years, malaria in pregnancy is more common in younger women who are pregnant compared with older pregnant women, in women who are pregnant for the first or second time (primigravidae or secundigravidae) compared with subsequent pregnancies, and in women with HIV compared with healthy women. [12] Malaria infection during pregnancy causes an enormous risk to the mother, fetus, and neonates.[9] Indeed although malaria during pregnancy might be asymptomatic due to a high level of acquired immunity in mothers residing in high transmission areas, it is still associated with an increased risk of maternal anemia, spontaneous abortion, stillbirth, prematurity, and low birth weight. [13] [14] [15] Moreover, severe maternal anemia increases the mother's risk of death. Malaria related anemia is estimated to cause as many as 10,000 maternal deaths each year in Africa. [16]

3. AETOLOGY AND RISK FACTORS

Humans acquire malaria from sporozoites transmitted by the bite of infected female anopheles mosquitoes. [17] Of about 3200 mosquito species so far described, some 430 belong to the genus anopheles. Of these, about 68 anopheles species are known to transmit malaria, with about 40 species considered important vectors. [18] When foraging, blood thirsty female anopheles mosquitoes fly upward searching for the scent trail of an attractive host. [19] Female anopheles are attracted to their human hosts over a range of 7 to 20m through a variety of stimuli, including exhaled carbon dioxide, lactic acid, other host odors , warmth and moisture. [20] Larger people tend to be bitten by mosquitoes more than smaller individuals.[16] Women receive significantly more mosquito bites in trials than men. Children secrete lower levels of chemical attractants than adults and, therefore, usually receive fewer mosquito bites than adults.[21] Malaria transmission does not occur at temperature less than 16 degree or greater than 35 degree or at altitudes greater than 3000m above sea level at the equator(lower elevations in cooler climates) because sporozoite development in the mosquito cannot take place. The optimal conditions for the transmission are humidity greater than 60% and an ambient temperature of 25 to 30. [22] Most of the important vectors of malaria breed in small temporary collections of fresh surface water exposed to sunlight and with little

predation, and in sites such as residual pools in drying river beds. Although rainfall provides breeding sites for mosquitoes, excessive rainfall may wash away mosquito larvae and pupae. Conversely, prolonged droughts may be associated with increased malaria transmission if they reduce the size and flow rates of large rivers sufficiently to produce suitable Anopheles breeding sites.[23] Anopheles mosquitoes vary in their preferred feeding and resting locations, although most bite in the evening and at night. The Anopheles mosquito will feed by day only if unusually hungry. Anopheles adults usually fly not more than 2 to 3 km from their breeding sites, although a flight range of up to 7 km has been observed. One cross-sectional study of about 7000 children under the age of 10 years found that, during months of peak transmission, living within 3 km of an Anopheles breeding site significantly increased the risk of malaria compared with living 8 to 10 km away (RR 21.00, 95% CI 2.87 to 153.00).[24] Very occasionally, strong winds may carry Anopheles up to 30 km or more.

In high transmission areas, pregnancy causes several physiological changes that make women more vulnerable. By weakening the immune system, pregnancy makes women more susceptible to malaria infection and increases their risk of illness, severe anemia and death. In addition, infected erythrocytes of P. falciparum can be sequestrated into the intravilli spaces of the placenta, thus preventing the placenta from ensuring its function appropriately.[25] Maternal risk factors for malaria in pregnancy include maternal age, ITN utilization, health education about prevention methods during pregnancy, gestational age, and gravidity.[9]

4. ETIOPATHOGENESIS AND PATHOPHYSIOLOGY OF MALARIA

Giuseppe Bastianelli, in Rome, recognized the existence of the P. falciparum responsible for malignant tertian fever. In 1894, Patrick Manson, in China, was the first one to hypothesize that the Plasmodium vector was a mosquito. This thesis was demonstrated in 1897 by Ronald Ross (Nobel Prize 1902), in India. In 1898, Anopheles species of mosquitoes were identified in Rome as the vector of the disease by Giovanni Battista Grassi, who described also the parasite cycle in the different species of Plasmodia. [26]

4.1.Plasmodium falciparum Life Cycle

As schematized in Fig. 1.1, P. falciparum life cycle involves stages either in mosquito vector (sexual reproduction) or in human host (asexual replication); where in particular the “blood stage” is responsible for much of the disease pathology. Parasites are transmitted to humans by the females of the Anopheles mosquito species. There are about 430 species of

Anopheles mosquitoes, but only 68 transmit malaria.[14][23] Anopheles gambiae, found in Africa, is one of the major malaria vectors. It is long living, prefers feeding on humans, and lives in areas near human habitation. [27] The intensity of malaria parasite transmission varies geographically according to vector species of Anopheles mosquitoes. Risk is measured in terms of exposure to infective mosquitoes, with the heaviest annual transmission intensity ranging from 200 to >1,000 infective bites per person. Interruption of transmission is technically difficult in many parts of the world because of limitations in approaches and tools for malaria control.

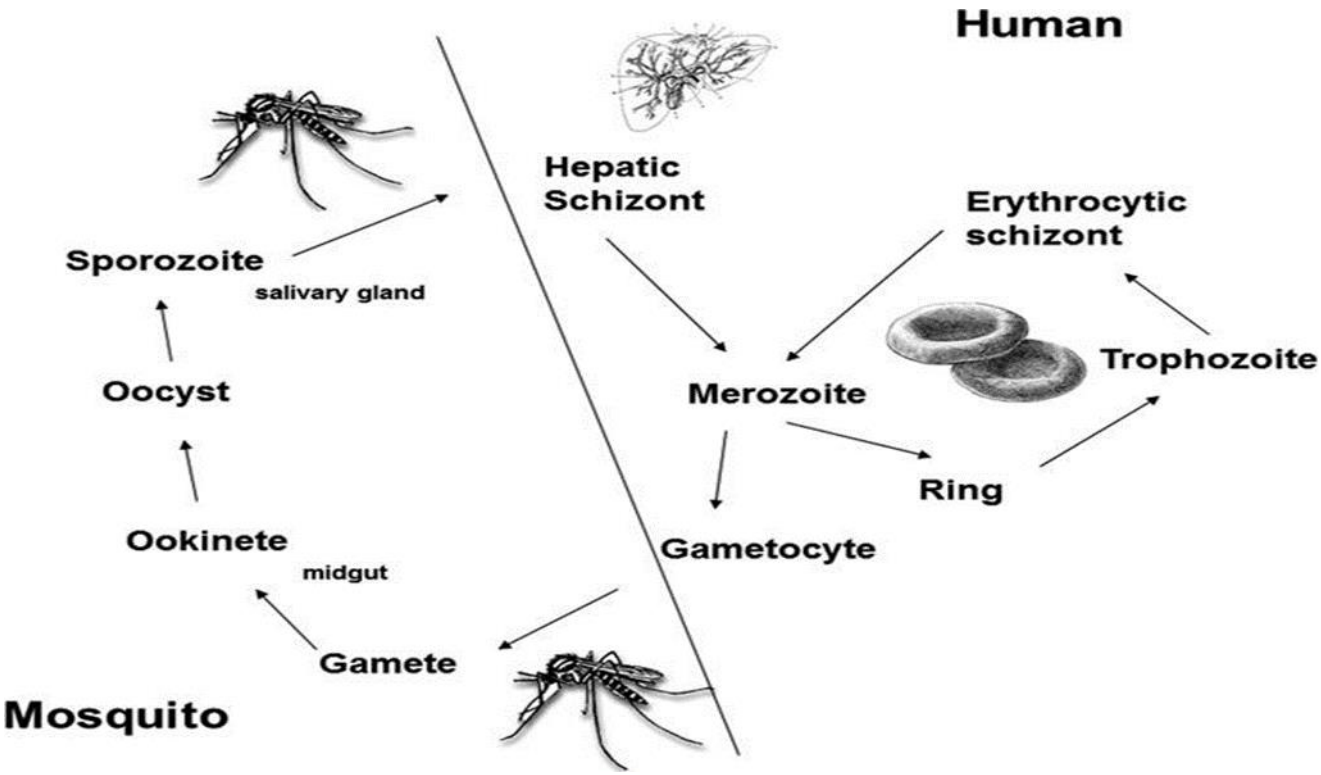

Figure 1: Plasmodium falciparum life cycle; [36]

P. falciparum life cycle involves either stage in mosquito vector (sexual reproduction) or in human host (asexual replication). The “blood stage” is responsible for much of the disease pathology in humans

The malarial infection begins when the sporozoite stage of the parasite that resides within the salivary gland of the mosquito halts in the host liver. This happens when an infected female bites a healthy person and takes its blood meal, injecting a small amount of saliva into the skin wound. Male mosquito does not feed on blood, hence only female serves as a vector. The saliva contains anti-hemostatic and anti-inflammatory enzymes disrupting the clotting process

and inhibiting the pain reaction. Typically, each infected bite contains 5–200 sporozoites which proceed to infect the human vector. Sporozoites stay for prolonged time in the skin before reaching the blood stream. Only the parasites surviving to phagocytes can rapidly enter the human bloodstream through a blood vessel, where they circulate for a matter of minutes before infecting liver cells. [28]

4.2.Liver Stage In Man

After circulating in the bloodstream, the sporozoites migrate to the liver and finally infect a hepatocyte, after crossing several Kupffer cells and hepatocytes. [29]The sporozoites rapidly grow in size absorbing nourishment to form a large round schizont. The schizont divides by schizogony, a type of asexual reproduction, in which multiple fissions result in the formation of a number of small, spindle-shaped uninucleate cells called merozoites.[26] After schizonts rupture, merozoites are released into the sinusoids or venous passages of the liver. This phase of asexual reproduction is called pre-erythrocytic schizogony. The merozoites are immune to medicines and host natural resistance. After a development stage in liver, during which there are no clinical symptoms of the disease, merozoites are released into the blood and enter the erythrocytic portion of their life cycle. A single schizont can produce thousands of merozoites by asexual reproduction.

In P. falciparum and P. malariae, schizont development and rupture occur rapidly, and merozoites can begin the erythrocyte invasion 1 or 2 weeks after the invasion of hepatocytes. This phase of the cycle is different in P. ovale and in P. vivax where parasites can stay in the liver as dormant cells (hypnozoites) for months or years before returning to schizont form and relapse the initial infection. [30]

The invasion of erythrocytes by merozoites involves some proteins originating from both parasites and RBCs. In particular, major merozoite surface proteins (MSP)-1 and -9 bind to erythrocyte band 3 protein [31], the merozoite orients its apical end towards the erythrocyte surface through merozoite apical membrane antigen-1 transmembrane protein and penetrates in the RBC involving erythrocyte binding antigens and the P. falciparum reticulocyte-binding homologs, which binds glycophorins and other unknown receptors. In P. vivax, reticulocyte invasion occurs after interaction with the Duffy blood group antigen, the erythrocyte receptor for the chemokine Interleukin-8/CXCL8. This antigen is generally missing in African population that is why P. vivax results more common in tropical areas other than Africa, such as Southern Asia and Malaysia. [32] By invading the erythrocytes, the merozoites initiate the

blood stage of the asexual cycle. The blood stage takes around 48 h to be completed. During this period, the parasites develop through several stages (ring, trophozoite, and schizont forms, respectively), characterized by different structures and specialized stage-specific features. [33]

4.3.Erythrocytic stage in man

The merozoites feed on erythrocytes, become rounded and gradually modify into trophozoites. During growth, a vacuole appears in the center of merozoites and the nucleus is pushed to one side; this modification that is known as “ring stage gives it a ring-like appearance in Giemsa-stained blood smears. The parasite by its cytostome feeds on hemoglobin and other nutrient taken from the plasma. The food vacuole secretes some digestive enzymes, which break down hemoglobin into proteins and hematin. Proteins are used by the parasite as nourishment source, whereas hematin is converted into a waste product called hemozoin (Hz).

As the ring form of the parasite enlarges, it begins to synthesize some stage specific molecules, which can be exported into the RBC, modifying the RBC membrane which now begins to adhere to the linings of visceral and other blood vessels, including those of the placenta. [34] The parasite eventually grows into the more rounded trophozoite form. During this stage; most active feeding, growth, and RBC modifications occur. New molecules are exported into the RBC: some of them assemble into flat membranous sacs of various forms, including Maurer’s clefts, which are visible in stained smears. Other proteins interact with the RBC membrane and cytoskeleton to form small knobs on its surface. Some molecules such as P. falciparum erythrocyte membrane protein (Pf EMP) 1 allow the infected RBC to adhere to the vascular endothelium, thus counteracting the action of immune defenses aimed at removing parasites from the blood stream through the spleen. As a consequence of infected RBC cytoadherence to brain–blood vessel walls, some malaria complications may occur, including cerebral malaria [35]and placental malaria.[34] Other exported molecules increase RBC permeability to nutrients. The parasite continues feeding on hemoglobin, and the heme products derived from hemoglobin digestion are converted into dark crystal particles to form the malarial pigment (Hz), which is scattered within the digestive vacuole. [36]

During their growth, the trophozoites metamorphose into schizonts.[26] Schizonts appear after a period of about 36–40h of growth and represent the full-grown trophozoites. Schizonts carry out some nuclear divisions and an intense synthesis and assembly of molecules to

organize RBC invasion. The nucleus of the schizont divides in the following 6–8 h to form from 12 to 24 daughter nuclei of new merozoite cells in the erythrocyte. This phase of asexual multiplication is known as erythrocytic schizogony. Finally, the RBC membrane and parasitophorous vacuolar membrane are lysed through a protease-dependent process [41] and the merozoites burst from the RBC, proceeding to infect other erythrocytes.

Free merozoites are very small (1.2 mm of length). Still, they contain all the tools deemed necessary to invade new RBCs as detailed by Bannister and Mitchell.[37] A single erythrocytic cycle is completed in 48 h (see Fig.2). Parasite remains in the bloodstream for roughly 60 s before entering into another erythrocyte, restarting the process. [37]

The infection cycle occurs in a highly synchronous fashion, with roughly all of the parasites throughout the blood at the same stage of development. The toxins are liberated into the blood along with the liberation of merozoites and then deposed into the liver and the spleen or under the skin, so that the host gets a sallow color.

The accumulated toxins cause malaria fever: the patient suffers from chills, shivering, sweating, high temperature headache, abdominal and back pain, nausea, diarrhea, and sometimes vomiting. The fever lasts for 6–10h and then it comes again after every 48h with the liberation of a new generation of merozoites. During the erythrocytic stage, some merozoites increase in size to form two types of gametocytes, the macrogametocytes and microgametocytes. The macrogametocytes (female) are large, round with the food-laden cytoplasm and a small eccentric nucleus. The microgametocytes (male) are small, with clear cytoplasm and a large central nucleus. This process is called gametocytogenesis. The specific factors underlying this sexual differentiation are largely unknown. The gametocytes take roughly 8–10 days to reach full maturity and do not develop further until they get sucked by the appropriate species of mosquito. If this does not happen, they degenerate and die, since they require lower temperature for further development. [38]

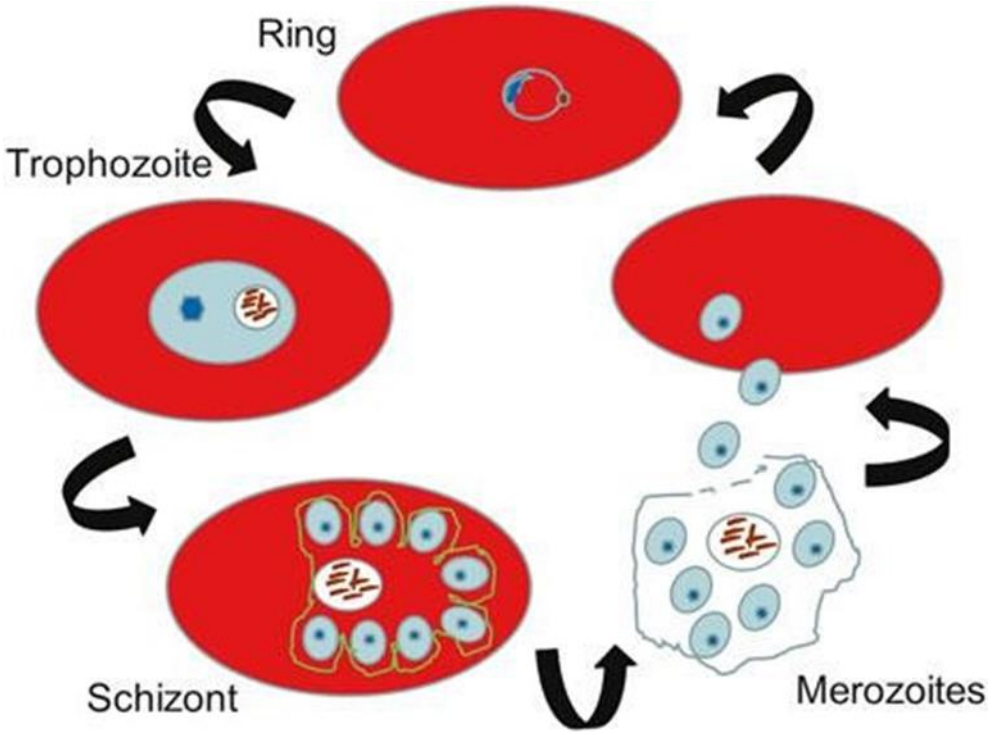

Figure 2: **Plasmodium falciparum erythrocytic cycle; the merozoites infect the erythrocyte and modify into "ring stage." The ring form of the parasite enlarges and grows into the trophozoite form.** [27]

The parasite converts hemoglobin into dark crystal particles to form the malarial pigment (Hz). The trophozoites metamorphose into schizonts that divide to form daughter nuclei of new merozoite cells in the erythrocyte. Finally, the merozoites burst from the RBC, proceeding to infect other erythrocytes.

4.4.Life cycle in mosquito

When a female Anopheles sucks the blood of a malaria patient, the gametocytes enter along with blood, reaching the stomach and leading to formation of gametes. [39] Only the gametocytes survive inside the stomach, while the other forms of the parasites, as well as the erythrocytes, are digested. Two types of gametes are formed: microgametocyte (male) and the macrogametocyte (female). The microgametocytes become active and their nucleus divides to produce 6–8 haploid daughter nuclei. The nuclei arrange at the periphery. The cytoplasm gives out the same number of flagella-like projections. A daughter nucleus enters in each projection. These projections separate from the cytoplasm. This process of formation of microgametes is called exflagellation. From each microgametocyte, 6–8 flagella-like active

microgametes are formed. The megagametocyte undergoes some reorganization and forms the megagametes. Fertilization of the female gamete by the male gamete occurs rapidly after gametogenesis. The fertilization event produces a zygote that remains inactive for some time and then elongates into a worm-like ookinete. The zygote and ookinete are the only diploid stages. The ookinete penetrates the wall of the stomach and comes to lie below its outer epithelial layer. It gets enclosed in a cyst formed partly by the zygote and partly by the stomach of mosquito. The encysted zygote is called oocyst.

The oocysts absorb nourishment and grow to about five times in size. They protrude from the surface of the stomach as transparent rounded structures. Over a period of 1–3 weeks, the oocyst grows to a size of tens to hundreds of micrometers. During this time, multiple nuclear divisions occur. As a consequence of oocyst maturation, the oocyst divides to form multiple haploid sporozoites. Each oocyst may contain thousands of sporozoites and groups of sporozoites get arranged around the vacuoles. This phase of asexual multiplication is known as sporogony. In the mosquito, the whole sexual cycle is completed in 10–21 days. Finally, the oocyst bursts and sporozoites are liberated into the hemolymph of the mosquito. They spread throughout the hemolymph and eventually reach the salivary glands and enter the duct of the hypopharynx. The mosquito now becomes infective and the sporozoites get inoculated or injected into the human blood when the mosquito bites, starting a new life cycle. It is estimated that a single infected mosquito may contain as many as 200,000 sporozoites.[39]

4.5.Placenta malaria pathophysiology

Malaria susceptibility increases during pregnancy, making these women an important parasite reservoir in the community. In stable transmission zones, malaria during pregnancy has a unique epidemiology characterized by parity-dependent susceptibility: primigravidae women are infected more frequently and with higher placental parasite densities than multigravidae women.[40] A prominent feature of P. falciparum malaria during pregnancy is the accumulation of parasites in the placenta, whereas parasite density in the peripheral circulation is low or undetectable for decades, the increased susceptibility to malaria during pregnancy was attributed to immunological changes associated with pregnancy and by the higher attractiveness of pregnant women to mosquitos, but this could not explain the reduction in infection rate and placental parasite burden over successive pregnancies. [40] An alternative molecular model to explain parity-dependent susceptibility is based on the ability of P. falciparum infected erythrocytes (IEs) to adhere to specific receptors, that is, chondroitin

sulphate A (CSA) on the vascular endothelium and thereby sequester in deep vascular beds in the placenta. They rarely bind to the other two commonly described receptors in non-pregnant individuals, i.e. CD36 and the intracellular adhesion molecule (ICAM-1). In pregnancy, the parasite antigens expressed on infected erythrocytes are collectively known as variant surface antigen pregnancy associated malaria (VSAPAM). They are different from those expressed in non-pregnant individuals and in stable transmission settings are not recognized by the immune system, explaining the higher risk in primigravidae. The binding of the variant surface antigen (VAR2CSA) with chondroitin sulphate A has been implicated in the pathology of falciparum malaria in pregnancy. The VAR2CSA belongs to the family of the erythrocyte membrane protein (PfEMP1), is encoded by the var2csa gene and its expression has been described in pregnant women with falciparum malaria. Levels of anti-VAR2CSA specific IgGs increase with parity, cannot be found in men and are associated with a favorable pregnancy outcome, so that the malaria risk decreases with increasing parity. Besides the antibody responses to VSAPAM, cytokine responses such as Th1, Th2, interleukins, TNF and regulators, IFN gamma, and monocytes have been observed in pregnant women with malaria. Rosetting, a phenomenon consisting of parasite-free erythrocytes surrounding parasite-infected erythrocytes and commonly observed in non-pregnant individuals, has been implicated in the pathogenesis of severe malaria but is uncommon in pregnant women with falciparum malaria.

The sequestration of P. vivax in the placenta, though until recently thought not to occur, has been described, with the involvement of ICAM-1 and CSA as receptors.

The effects of hormonal changes on pregnancy associated malaria have been described in few studies and are subject to debate. Increased cortisol levels have been associated with increased risk of malaria in pregnant women.

The increased attractiveness of pregnant women to mosquitoes may be explained by physiological and behavioral changes occurring during pregnancy. Physiological changes include increased exhaled breath and increased abdominal temperature that may render pregnant women more easily detectable by mosquitoes. Behavioral changes are represented by the fact that pregnant women urinate twice as frequently as non-pregnant women, resulting in an increased exposure to mosquito bites at night because they have to leave the protection of their bed nets.

Malaria-associated placental changes have been described for stable and unstable transmission settings. They include presence of parasites, inflammatory changes and

hemozoin (pigment) deposition. Placental changes have been characterized into four levels, i.e. acute (parasites present, malaria pigment absent), chronic (parasites and malaria pigment present), past infection (no parasite but pigment present) and no infection (both parasites and malaria pigment absent). [41]

It is unclear what the mechanism at the basis of malaria-related preterm delivery is, though fever, anemia, and high levels of TNF alpha or interleukin 10 have been identified as important risk factors.

LBW due to IUGR is associated with maternal anemia and elevated levels of cytokines. Although the exact mechanism has not been elucidated, it appears to be due to chronic infections that cause reduced fetal circulation and placental insufficiency. Placental endocrine changes related to falciparum infection have been suggested as another possible mechanism leading to IUGR.[41]

5. CLINICAL FEATURES OF UNCOMPLICATED AND SEVERE MALARIA

5.1. Uncomplicated malaria

The interval from the time of infection until the parasites become detectable in the blood is termed prepatent period, while the term of incubation period is defined as the interval between infection and the onset of symptoms. The duration of incubation period is influenced by several factors such as the species of infecting parasites, the way of parasite transmission, the degree of previous immune status of the host, the chemoprophylactic use of antimalarial drugs, and probably the density of parasite inocula. Incubation period ranges from 9 to 30 days with P. falciparum infections, tending to present the shortest, and P. malariae the more prolonged times. In most of P. falciparum and P. vivax malaria, the incubation period is approximately two weeks. In blood-induced infections, the incubation period is usually shorter with symptoms developing within 10 days of transfusion for P. falciparum, 16 days for P. vivax, and 40 days or longer for P. malariae.[58,61][42][43] As far as the degree of previous protection possessed by the infected subject is concerned, it is known that effective immunity prolongs incubation period and reduces level of parasitemia and clinical manifestations.

Low asymptomatic parasitemia may persist in migrants from endemic areas long after their arrival in the host country,[58] and delayed clinical presentation of P. falciparum have been

described as long as [44] 4 or even 8 years [45] after subjects have left malaria-endemic areas. Pregnancy and co-infection with HIV have been associated with late presentation of malaria caused by P. falciparum in immigrants.

Prolonged incubation period may also be caused by the use of antimalarial drugs that, although ineffective, may impact on the parasite multiplication rate. The clinical manifestations of malaria are dependent on the previous immune status of the host. In areas where endemicity of P. falciparum malaria is stable, severe malaria most commonly occurs in children up to 5 years of age, while is less common in older children and adults because of the acquisition of partial immunity. In areas of lower endemicity, the age distribution of severe malaria is less well defined and may also occur in adult semi-immune persons.

The first symptoms of malaria, common to all the different malaria species, are nonspecific and mimic a flu-like syndrome. The hallmark of malaria is fever. Up to two days before the onset of fever, prodromal symptoms, such as malaise, anorexia, lassitude, dizziness, with a desire to stretch limbs and yawn, headache, backache in the lumbar and sacroiliac region, myalgias, nausea, vomiting and a sense of chillness may be experienced. [42] The fever is usually irregular at first and the temperature rises with shivering and mild chills. After some days fever tends to become periodic depending on the synchronized schizogony. In fact, for unknown reasons development of asexual blood stage parasites becomes synchronous after some days with a periodicity depending on the length of the asexual cycle.

5.1.1. Plasmodium vivax and Plasmodium ovale

In P. vivax and P. ovale infection, if left untreated, asexual cycles become synchronous after 5 to 7 days causing periodic febrile paroxysms. The classical malaria paroxysm presents three stages: a cold stage, followed by a hot stage with a terminal sweating stage. The cold stage is typically characterized by a sudden onset with a feeling of extreme coldness. The subject may shiver and his or her teeth may chatter. In virtue of an intense peripheral vasoconstriction phenomenon, the skin is cold, dry, pale, cyanosed and sometimes goose-pimpled. [58,61] The subject feels the need to cover himself with all available blankets he can reach, but without obtaining comfort. During this initial stage, that usually lasts 10- 30 minutes and only occasionally up to 90 minutes, the temperature rises gradually to a peak (usually between 39° and 41° C). Eventually, the shivering ceases and the second or hot stage start. The skin is now hot and dry and the face flushed, with the subject that feels heat and

discards blanket. The temperature may further rise and reach hyperpyrexial levels. Vomiting is common in this phase and sometimes diarrhea, severe retro-orbital headache, parched throat, extreme thirst, and altered consciousness are also present. In young children convulsion may occur. Within 2-6 hours, the subject enters the third stage of the paroxysm, the sweating stage, with sudden profuse sweating, appearing first at the temples, and rapidly becoming generalized and copious. The temperature falls rapidly and the subject feels well, although extremely tired, and usually falls asleep. The sweating stage lasts 2 to 3 hours, with the entire paroxysm, which more frequently begins in late afternoon or evening, lasting 6-10 hours.

At the physical examination, splenomegaly may be present during the acute attack but is more commonly observed after the second week of the attack. Rupture of an enlarged spleen is a possible, although rare, complication. The liver may also be enlarged and palpable.

In P. vivax and P. ovale infection, schizogony occurs every 48 hours so that the febrile paroxysm occurs every third day (tertian fever). During the intervals between febrile paroxysms, the subject is usually afebrile and feels well. If left untreated, the attacks may last from a few weeks to some months and then spontaneously and gradually resolve. In P. vivax and P. ovale infection, after a quiescent or latent period, relapse may occur with renewal of clinical symptoms and asexual parasitemia. This phenomenon is due to reinvasion of the blood by merozoites produced when hypnozoites awake from dormancy and develop into hepatic schizont. Relapses occur weeks, months, or even years after the primary infection with different timing related to the P. vivax strain, geographical origin of the infection and the previous use of inadequate antimalarial treatment. From the clinical point of view, relapse is similar to the first attack, except for a more abrupt onset and the absence of the initial period of irregular fever, as the infection is more synchronous. The relapse is usually less severe and of shorter duration than the first attack.

Infections with P. vivax and P. ovale are rarely complicated. However, there is increasing evidence of serious and fatal complications due to P. vivax infection. [46]

5.1.2. Plasmodium Falciparum

In P. falciparum malaria, the set of fever occurs after few days of prodromal symptoms started during the last days of the incubation period (normal range 9-14 days). At first, fever is irregular, but usually occurs daily. It may be intermittent or continuous, and shows no sign of periodicity until the illness has continued for a week or more. The symptoms present in the

prodromal phase continue and increase, so configuring a flu-like syndrome. Anorexia, dyspepsia, epigastric discomfort, nausea, vomiting and watery diarrhea are frequent and may be misdiagnosed as a gastrointestinal infection. Herpes labialis may be present. A dry cough and an increase in the respiration rate may be observed, arising the suspect of an acute respiratory infection. Other non-specific physical findings are tender hepatosplenomegaly, orthostatic hypotension, and some degree of jaundice. The pulse may be rapid (100 to 120 beats/min) and the blood pressure may be low (90-100 mmHg, systolic).[63] [47] When periodic febrile paroxysms occur, they may be daily (quotidian), every third day (tertian) or at about 36-hour intervals (subtertian).

Although the subject may not appear very ill, serious complications may develop at any stage. In non-immune people P. falciparum malaria may progress very rapidly to severe malaria unless appropriate treatment is started. If the acute attack is rapidly diagnosed and adequately treated, the prognosis of falciparum malaria is good, even if complications may still occur. The response to treatment is usually rapid with resolution of fever and most symptoms within 3 days.

Recrudescence with renewal of clinical manifestation and/or parasitemia, due to persistent erythrocytic forms, may occur.

5.1.3. Plasmodium malaria

P. malariae causes the mildest and most persistent form of malaria infection. After an incubation period that is never less than 18 days, but that may be up to 30-40 days, prodromal symptoms resembling those of vivax malaria proceeds the onset of fever. The clinical picture of the primary attack is similar to that of vivax malaria. The onset is often insidious, but febrile paroxysms, often occurs in the late afternoon, show well synchronized schizogony from an early stage and is typically separated by intervals of 72 hours (quartan malaria).

Representatives of all developmental forms of the asexual parasite are usually present. Left untreated, the acute attack is self-limiting but may last for several months before spontaneous remission occurs.[41] Severe complications of P. malariae infection are rarely observed. However, recrudescences may occur, more frequently during the first year and then at longer intervals, even after 30-50 years. P. malariae has no hypnozoite form, so recrudescences arise from persisting blood stage. Asymptomatic P. malariae parasitemia in blood donors may cause transfusion malaria.

P. malariae parasitemia in blood donors may cause transfusion malaria. P. malariae infection is associated with development of a nephrotic syndrome. First clinical manifestation often onsets before 15 years of age. Classically, edema and ascites are present and accompanied by laboratory evidence of heavy proteinuria, hypoalbuminemia and hyperlipidemia. P. malariae parasitemia is common in children, but not in adults.

Transient clinical remissions with period of asymptomatic proteinuria are frequent but progressive deterioration and development of renal failure often occur within 3 to 5 years.

5.1.4. Plasmodium knowlesi

P. knowlesi is the species of plasmodium most recently identified as agent of human malaria.[48] Until few years ago, it was known as agent of chronic infection of the longtailed (Macaca fascicularis) and pig-tailed (Macaca nemestrina) macaques.[65][49] P. knowlesi malaria is the most common locally acquired human malaria in Malaysian Borneo (~70% of malaria cases),[50] with the disease also reported from other countries of southern and eastern Asia. On the basis of clinical features, it is not possible to distinguish knowlesi malaria from vivax or falciparum malaria.[66] The development of hyperparasitemia and other complications are fairly common.[66][50] Concerning diagnosis, the identification of P. knowlesi infection by using microscopy only is difficult because it is very similar to P. malariae. Polymerase Chain Reaction (PCR) is currently the method of choice to obtain a certain diagnosis.[64][47][51]

5.2 Severe Malaria

Most of the severe malaria complications occur in non-immune subjects with falciparum malaria and involve central nervous system (cerebral malaria), pulmonary system (respiratory failure), renal system (acute renal failure) and/or hematopoietic system (severe anemia). As the progression to these complications can be rapid and severe malaria is a potentially fatal disease, any malaria patient must be assessed and treated rapidly, and frequent observations are needed to look for early signs of systemic complications.[58] [47]According to the most recent definition by World Health Organization (WHO), in a patient with P. falciparum asexual parasitemia and no other obvious cause of symptoms, the presence of one or more of the clinical or laboratory features reported in Table 1, classifies the patient as suffering from severe malaria.[2] [2] This definition has been proposed to assist clinical and epidemiological

descriptions. In clinical practice, any subject for whom severe malaria is suspected must be treated as having severe malaria, although not clearly fulfilling the proposed WHO criteria.

5.2.1 Cerebral malaria

In order to allow comparability of clinical and therapeutic findings, a strict definition of cerebral malaria was recommended.[67][52]In accordance to the most recent WHO definition, cerebral malaria is a severe P. falciparum malaria with cerebral manifestations, usually including coma (Glasgow coma scale < 11, Blantyre coma scale < 3). Malaria with coma persisting for > 30 minutes after a seizure is considered to be cerebral malaria. [53] However, in clinical practice, subjects with any degree of altered consciousness and any other sign of cerebral dysfunction should be treated for severe malaria. Clinical evolution and neurologic findings are highly variable. Coma may onset suddenly or gradually, with initial drowsiness (always worrying symptom), confusion, disorientation, delirium or agitation[58,61,67] [47], [52]Subjects with cerebral malaria may be open-eyed but nonseeing, and present with disconjugate gaze and nystagmus. Sustained ocular deviation, generally upward or lateral, may be observed. They may exhibit various forms of abnormal posturing, including decerebrate rigidity (extensor posturing, with arms and legs extended), decorticate rigidity (extensor posturing, with arm flexed and legs extended), and opisthotonos. Neck rigidity and photophobia are rare symptoms, but some resistance to passive neck flexion, in absence of other signs of meningeal irritation, is not uncommon. Seizures, generalized or sometimes focal, are common, particularly in children. Electroencephalographic abnormalities are non-specific. When lumbar puncture is performed in order to differentiate cerebral malaria from other causes of encephalopathy, the cerebral spinal fluid (CSF) is clear and shows a mild lymphocyte pleocytosis (rarely more than 10 cells/μl), and increased protein concentrations (rarely exceeding 150 mg/dL). The blood/CSF glucose ratio is normal, while the lactate concentration of lactate is raised. Examination of fundus may evidence retinal hemorrhages (6-37% of cases), while papilledema is rarely seen in cerebral malaria. [51]

If left untreated, cerebral malaria is probably nearly always fatal. Even when treated, cerebral malaria has an approximate 20% of mortality rate in adults and 15% in children. Among subjects who survive, the recovery is relatively rapid with complete reversibility of neurological signs and symptoms. However, neurological sequelae may occur. The most common manifestations are psychosis, cranial nerve lesions, extrapyramidal tremor, ataxia, polyneuropathy and seizures. Most of these neurologic disturbances are transient, resolving

few days to several weeks after their onset. In some cases, particularly in children, residual neurological deficit may occur after severe malaria. Language disorder, motor deficits, cognitive impairments and epilepsy have been reported in childhood following recovery from cerebral malaria.[69][54]

5.2.2 Respiratory failure

Respiratory failure may rapidly develop at any stage of acute malaria but, in many cases, occurs when subjects are already recovering, parasitemia is cleared, and in comatose subjects, consciousness has been regained. [47] Pregnant women are particularly prone to develop acute respiratory failure. The clinical picture is indistinguishable from the adult respiratory distress syndrome that develops as a result of a systemic or pulmonary infection, severe trauma or other systemic or pulmonary insults. Tachypnea, dyspnea, and scattered rales and ronchi on auscultation are the earliest warnings. Patients with severe hypoxemia may require mechanical ventilation.

5.2.3 Acute renal failure

While biochemical evidence of renal dysfunction is frequently observed in otherwise uncomplicated malaria, acute renal failure is another complication of falciparum malaria, much more common in adults than among children. Malaria acute renal failure may be defined as a urine output of <400 mL in 24 h in adults, or 12 mL/kg in 24 h in children, in spite of rehydration, and a serum creatinine of more than 265μmol/l (>3.0 mg/dL). In practice for initial assessment, the serum creatinine alone is used.[51][53] Acute renal failure may be present at the subject admission in a context of a multiple organ involvement, or occurring in the recovery phase of severe malaria. In the former case prognosis is worse. Oliguria is the main feature of acute renal failure, although urine output may also be normal or increased. In oliguric patients, levels of blood urea nitrogen and serum creatinine are elevated and hyperkaliemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis usually develop. Dialysis may be necessary in some cases.

5.2.4 Jaundice and hepatic dysfunction

Jaundice is common in adult subjects with severe malaria, while relatively rare in children. It is generally mild or moderate, but in some cases may be marked. Among the jaundiced subjects, hyperbilirubinemia may be predominantly unconjugated, in case of

extensive hemolysis of both parasitized and unparasitized erythrocytes, or conjugated, indicating hepatocytic disfunction. Apart from jaundice, signs of severe liver cell damage are uncommon. Concentrations of transaminases may be increased up to ten-fold, but never to the level observed in viral hepatitis. The liver, as well as the spleen, is enlarged and tender, especially in young children and non-immune adults.

5.2.5 Severe anemia

Severe malaria is associated with development of anemia, usually normochromic and normocytic. However, in endemic areas the morphology may be influenced by the nutritional status of the subject and some helminthiasis, resulting in an associated microcytic (iron deficiency) and macrocytic (folic acid deficiency) component. The causative mechanisms are multifactorial, including hemolysis of infected and uninfected red blood cells, inappropriate bone marrow response, and numerous other individual factors (e.g. bacteremia, HIV, hookworm, G6PD deficiency, vitamin A and vitamin B12 deficiency).[55] In areas of high endemicity, severe anemia is a particular problem in children, where it can be fatal. In epidemic rather than endemic areas, severe anemia may also develop in adult population and pregnant women, especially primiparae, are those at major risk. In accordance with the WHO definition, severe malarial anemia is defined in the presence of a hemoglobin level of <5g/dL or hematocrit <15%.[2] The UK malaria treatment guidelines define severe anemia when hemoglobin level is <8 g/dL. [52] Pathological consequences of anemia are particularly likely with such degree of anemia; however, they are also importantly related to the rapidity at which it develops. In this perspective, decisions regarding blood transfusion should be taken at individual level. Children with severe anemia and respiratory distress will benefit from transfusions that may be lifesaving. [2]

5.2.6. Hypoglycemia

Hypoglycemia has been detected in approximately 8% of adults and up to 30% of children with cerebral malaria. Hypoglycemia is a particular complication in pregnancy. It may be present before starting antimalarial treatment, representing a sign of poor prognosis. Hypoglycemia can also result from rapid infusions or prolonged treatment with quinine, due to its capability to stimulate insulin secretion. Early diagnosis is essential in order to assure a prompt treatment that may be lifesaving, but symptoms may be easily overlooked. In fact, classical symptoms of hypoglycemia, such as those induced by adrenaline secretion

(sweating, tachycardia, breathlessness, tremor, anxiety and hunger) or those due to dysfunction of central nervous system (impairment of consciousness, seizures, extensor posturing), are difficult to distinguish from those caused by malaria. Any subject with malaria and altered behavior or consciousness, or seizure, should be evaluated immediately for blood glucose level and, if this cannot be possible, assumed as hypoglycemic and given glucose.

5.2.7. Blackwater fever

Blackwater fever is a syndrome presenting with passage of mahogany-colored (or „Coca-Cola"-colored) urine in association with severe intravascular hemolysis. The dark urine is due to hemoglobinuria. [53] Blackwater fever occurs in subjects with G6PD deficiency who takes antioxidant drugs or foodstuffs, in subjects with G-6PD deficiency who have acute malaria after the administration of quinine or artemisinin derivative, but also in subject with acute, often severe malaria, who have normal red cell G-6PD concentrations. [56] Blackwater fever usually resolves on its own without complications. Only a minority of subjects may develop acute renal failure as a consequence of acute tubular necrosis.[44] [57]

Table: Clinical and laboratory features of severe malaria [54]

Clinical features:
- impaired consciousness or unrousable coma
- prostration, i.e. generalized weakness so that the patient is unable walk or sit up without assistance
- failure to feed
- multiple convulsions (more than two episodes in 24 h)
- deep breathing, respiratory distress (acidotic breathing)
- circulatory collapse or shock, systolic blood pressure < 70 mmHg in adults and < 50 mmHg in children
- clinical jaundice plus evidence of other vital organ dysfunction
- hemoglobinuria
- abnormal spontaneous bleeding
- pulmonary edema (radiological)

Laboratory findings:
- hypoglycemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- Severe normocytic anemia (Hb < 5 g/dl, packed cell volume < 15%)
- hemoglobinuria
- hyperparasitaemia (> 2% or 100,000/µl in low intensity transmission areas or > 5% or 250,000/µl in areas of high stable malaria transmission intensity)
- hyperlactataemia (lactate > 5 mmol/l)
- renal impairment (serum creatinine > 265 µmol/l)

6. DIAGNOSIS OF MALARIA

Prompt and accurate diagnosis is critical to the effective management of malaria in pregnancy. The global impact of malaria has spurred interest in developing effective diagnostic strategies not only for resource-limited areas where malaria is a substantial burden on society, but also in developed countries, where malaria diagnostic expertise is often lacking. [4,5] Malaria diagnosis involves identifying malaria parasites or antigens/products in patient blood. Although this may seem simple, the diagnostic efficacy is subject to many factors. The different forms of the 5 malaria species; the different stages of erythrocytic schizogony, the endemicity of different species, the interrelation between levels of transmission, population movement, parasitemia, immunity, and signs and symptoms; drug resistance, the problems of recurrent malaria, persisting viable or non-viable parasitemia, and sequestration of the parasites in the deeper tissues, and the use of chemoprophylaxis or even presumptive treatment on the basis of clinical diagnosis, can all influence the identification and interpretation of malaria parasitemia in a diagnostic test. Despite its large burden of disease, P. falciparum infection can be difficult to diagnose during pregnancy, particularly in semi-immune women who often are asymptomatic during infection. Although IEs accumulate in the placenta, parasite density in peripheral blood can be too low for detection by routine BS microscopy.

Malaria is a potential medical emergency and should be treated accordingly. Delays in diagnosis and treatment are leading causes of death in many countries [6]. Diagnosis can be

difficult where malaria is no longer endemic for healthcare providers unfamiliar with the disease. Clinicians may forget to consider malaria among the potential diagnoses for some patients and not order the necessary diagnostic tests. Technicians may be unfamiliar with, or lack experience with, malaria, and fail to detect parasites when examining blood smears under a microscope. In some areas, malaria transmission is so intense that a large proportion of the population is infected but remains asymptomatic, e.g., in Africa. Such carriers have developed sufficient immunity to protect them from malarial illness, but not infection. In such situations, finding malaria parasites in an ill person does not necessarily mean that the illness is caused by the parasites. In many malaria endemic countries, the lack of resources is a major barrier to reliable and timely diagnosis. Health personnel are undertrained, underequipped, and underpaid. They often face excessive patient loads, and must divide their attention between malaria and other equally severe infectious diseases, such as tuberculosis or HIV/AIDS.

6.1. Laboratory diagnosis of malaria

Rapid and effective malaria diagnosis not only alleviates suffering, but also decreases community transmission. The nonspecific nature of the clinical signs and symptoms of malaria may result in overtreatment of malaria or non-treatment of other diseases in malaria endemic areas, and misdiagnosis in non-endemic areas [15]. In the laboratory, malaria in pregnancy is diagnosed using different techniques, e.g. conventional microscopic diagnosis by staining thin and thick peripheral blood smears [16], rapid diagnostic tests e.g., OptiMAL , ICT , Para- HIT-f [10], ParaScreen , SD Bioline , Paracheck , and molecular diagnostic methods, such as polymerase chain reaction (PCR) .

6.1.1. Microscopic diagnosis using stained thin and thick peripheral blood smears (PBS)

Malaria is conventionally diagnosed by microscopic examination of stained blood films using Giemsa, Wright's, or Field's stains [25]. This method has changed very little since Laveran's original discovery of the malaria parasite, and improvements in staining techniques by Romanowsky in the late 1800s. More than a century later, microscopic detection and identification of Plasmodium species in Giemsa-stained thick blood films (for screening the presenting malaria parasite), and thin blood films (for species‟ confirmation) remains the gold standard for laboratory diagnosis [26]. Malaria is diagnosed microscopically by staining thick and thin blood films on a glass slide, to visualize malaria parasites. Briefly, the patient's finger is cleaned with 70% ethyl alcohol, allowed to dry and then the side of fingertip is picked with a sharp sterile lancet and two drops of blood are placed on a glass slide. To

prepare a thick blood film, a blood spot is stirred in a circular motion with the corner of the slide, taking care not make the preparation too thick, and allowed to dry without fixative. After drying, the spot is stained with diluted Giemsa (1:20, vol/vol) for 20 min, and washed by placing the film in buffered water for 3 min. The slide is allowed to air-dry in a vertical position and examination using a light microscope. As they are unfixed, the red cells lyse when a water-based stain is applied. A thin blood film is prepared by immediately placing the smooth edge of a spreader slide in a drop of blood, adjusting the angle between slide and spreader to 45 and then smearing the blood with a swift and steady sweep along the surface. The film is then allowed to air-dry and is fixed with absolute methanol. After drying, the sample is stained with diluted Giemsa (1:20, vol/vol) for 20 min and washed by briefly dipping the slide in and out of a jar of buffered water (excessive washing will decolorize the film). The slide is then allowed to air-dry in a vertical position and examined under a light microscope [27]. The wide acceptance of this technique by laboratories all around the world can be attributed to its simplicity, low cost, its ability to identify the presence of parasites, the infecting species, and assess parasite density -all parameters useful for the management of malaria. Recently, a study showed that conventional malaria microscopic diagnosis at primary healthcare facilities in Tanzania could reduce the prescription of antimalarial drugs, and also appeared to improve the appropriate management of non-malarial fevers [16]. However, the staining and interpretation processes are labor intensive, time consuming, and require considerable expertise and trained healthcare workers, particularly for identifying species accurately at low parasitemia or in mixed malarial infections. The most important shortcoming of microscopic examination is its relatively low sensitivity, particularly at low parasite levels. Although the expert microscopist can detect up to 5 parasites/μl, the average microscopist detects only 50-100 parasites/μl [28]. This has probably resulted in underestimating malaria infection rates, especially cases with low parasitemia and asymptomatic malaria. The ability to maintain required levels of in malaria diagnostics expertise is problematic, especially in remote medical centers in countries where the disease is rarely seen [29]. Microscopy is laborious and ill-suited for high-throughput use, and species determination at low parasite density is still challenging. Therefore, in remote rural settings, e.g. peripheral medical clinics with no electricity and no health-facility resources, microscopy is often unavailable [30].

6.1.2. Rapid diagnostic tests (RDTs)

Since the World Health Organization (WHO) recognized the urgent need for new, simple, quick, accurate, and cost-effective diagnostic tests for determining the presence of malaria parasites, to overcome the deficiencies of light microscopy, numerous new malaria diagnostic techniques have been developed [39]. This, in turn, has led to an increase in the use of RDTs for malaria, which are fast and easy to perform, and do not require electricity or specific equipment [40]. Currently, 86 malaria RDTs are available from 28 different manufacturers [41]. Unlike conventional microscopic diagnosis by staining thin and thick peripheral blood smears, and QBC technique, RDTs are all based on the same principle and detect malaria antigen in blood flowing along a membrane containing specific anti-malaria antibodies; they do not require laboratory equipment. Most products target a P. falciparum-specific protein, e.g. histidine-rich protein II (HRPII) or lactate dehydrogenase (LDH). Some tests detect P. falciparum specific and panspecific antigens (aldolase or pan- malaria pLDH), and distinguish non-P. falciparum infections from mixed malaria infections. Although most RDT products are suitable for P. falciparum malaria diagnosis, some also claim that they can effectively and rapidly diagnose P. vivax malaria. Recently, a new RDT method has been developed for detecting P. knowlesi [44]. RDTs provide an opportunity to extend the benefits of parasite-based diagnosis of malaria beyond the confines of light microscopy, with potentially significant advantages in the management of febrile illnesses in remote malaria-endemic areas. RDT performance for diagnosis of malaria has been reported as excellent; however, some reports from remote malaria-endemic areas have shown wide variations in sensitivity. Murray and co-authors recently discussed the reliability of RDTs in an “update on rapid diagnostic testing for malaria” in their excellent paper [49]. Overall, RDTs appears a highly valuable, rapid malaria diagnostic tool for healthcare workers; however, it must currently be used in conjunction with other methods to confirm the results, characterize infection, and monitor treatment. In malaria-endemic areas where no light microscopy facility exists that may benefit from RDTs, improvements are required for ease of use, sensitivity for non-falciparum infection, stability, and affordability. The WHO is now developing guidelines to ensure lot-to-lot quality control, which is essential for the community’s confidence in this new diagnostic tool [41]. Because the simplicity and reliability of RDTs have been improved for use in rural endemic areas, RDT diagnosis in non-endemic regions is becoming more feasible, which may reduce time-to-treatment for cases of imported malaria [30].

6.2.Molecular diagnostic methods

Traditional malaria diagnostic methods remain problematic. New laboratory diagnostic techniques that display high sensitivity and high specificity, without subjective variation, are urgently needed in various laboratories. Recent developments in molecular biological technologies, e.g. PCR, loop-mediated isothermal amplification (LAMP), microarray, mass spectrometry (MS), and flow cytometric (FCM) assay techniques, have permitted extensive characterization of the malaria parasite and are generating new strategies for malaria diagnosis.

6.2.1. PCR technique

PCR-based techniques are a recent development in the molecular diagnosis of malaria, and have proven to be one of the most specific and sensitive diagnostic methods, particularly for malaria cases with low parasitemia or mixed infection [55]. The PCR technique continues to be used extensively to confirm malaria infection, follow-up therapeutic response, and identify drug resistance [27]. It was found to be more sensitive than QBC and some RDTs [56,57]. Concerning with the gold standard method for malaria diagnosis, PCR has shown higher sensitivity and specificity than conventional microscopic examination of stained peripheral blood smears, and now seems the best method for malaria diagnosis [55]. PCR can detect as few as 1-5 parasites/μl of blood (≤0.0001% of infected red blood cells) compared with around 50-100 parasites/μl of blood by microscopy or RDT. Moreover, PCR can help detect drug-resistant parasites, mixed infections, and may be automated to process large numbers of samples [58,59]. Some modified PCR methods are proving reliable, e.g., nested PCR, real-time PCR, and reverse transcription PCR, and appear to be useful second-line techniques when the results of traditional diagnostic methods are unclear for patients presenting with signs and symptoms of malaria; they also allow accurate species determination [58,60-62]. Recently, the PCR method has become widely accepted for identifying P. knowlesi infections [63-65]. Although PCR appears to have overcome the two major problems of malaria diagnosis-sensitivity and specificity- the utility of PCR is limited by complex methodologies, high cost, and the need for specially trained technicians. PCR, therefore, is not routinely implemented in developing countries because of the complexity of the testing and the lack of resources to perform these tests adequately and routinely [66]. Quality control and equipment maintenance are also essential for the PCR technique, so that it

may not be suitable for malaria diagnosis in remote rural areas or even in routine clinical diagnostic settings [67].

7. TREATMENT OF MALARIA IN PREGNANCY

7.1.Intermittent Presumptive Treatment (IPTp)

7.1.1. IPTp-SP

MiP is associated with maternal anemia, LBW deliveries, PTD, and fetal loss. Severe maternal anemia increases the risk of maternal death, and both LBW and PTD increase the risk of infant death. To avoid these poor outcomes, measures to prevent PM have been recommended by the World Health Organization (WHO). The first agent used to prevent PM was weekly chloroquine (CQ) at a prophylaxis dose. However, the emergence of CQ-resistant parasites in sub-Saharan Africa during the 1980s prompted the search for new strategies. A 1992 study in Malawi showed that two treatment doses of SP given during the second and early third trimester significantly reduced the prevalence of PM compared with CQ (Schultz et al. 1994). A subsequent trial in Kenya confirmed that two SP treatment doses reduced PM prevalence in HIV infected women (Parise et al. 1998). In the early 2000s, WHO recommended intermittent presumptive treatment (IPTp) for pregnant women in malaria-endemic regions, with at least two curative doses of the antimalarial drug SP, one dose in the second and the other dose in the third trimester of pregnancy. In 2012, WHO updated the recommendation, increasing the number to three or more SP doses. In practice, women in areas of moderate high malaria transmission should receive SP at each antenatal care visit during the second and third trimesters (because four visits are recommended), with 1 mo intervals between doses (www.who.int/malaria/areas/preventive_thera pies/pregnancy/en). Owing to the spread of SP resistance in sub-Saharan Africa, artemisinin-based combinations (ACTs) were adopted as the first-line treatment for uncomplicated malaria in the 2000s (Eastman and Fidock 2009). Even as the general population was switching to ACT as treatment policy, the IPTp-SP strategy was being widely adopted for pregnant women. At present, WHO continues to recommend IPTp-SP, even in areas with high levels of SP resistance and treatment failure. Improved outcomes without an effect on parasitological measures are difficult to interpret. During the years 1992 – 2002, IPTp-SP significantly reduced PM in studies conducted across Africa. However, most data collected after 2001 – 2002 in East and Southeast Africa indicate that IPTp-SP lost its efficacy to reduce PM prevalence and/or parasite density. This trend has progressed to West Africa, where one site in Ghana reported that IPTp-SP did not reduce PM prevalence (van Spronsen et al. 2012). SP

resistance results from accumulating mutations in dhfr and dhps genes. The quintuple P. falciparum mutations (three in Pfdhfr and two mutations in Pfdhps) have been associated with treatment failure (Kublin et al. 2002; Naidoo and Roper 2013), and increased placental parasite density with an increasing number of Pfdhfr mutations (Mockenhaupt et al. 2007). A WHO document published in November 2015 (www.who.int/malaria/publications/atoz/istpand-act-in-pregnancy.pdf) stated that "An association between sextuple mutant haplotypes of P. falciparum and decreased birth weight has been reported in observational studies in a few sites in East Africa. Further studies are required to assess this and to devise the best and most cost-effective prevention strategies in areas of very high SP resistance." The policy of continuing IPTp-SP in areas of high resistance is puzzling and inconsistent with WHO directives for malaria treatment (Nosten and McGready 2015), as well as studies that strongly relate dhfr/dhps mutations to treatment failure. Currently, IPTp-SP remains efficacious for reducing the rate of PM and/or parasite burden at some sites in West Africa. However, even in areas with low or moderate SP resistance, the IPTp strategy does not completely prevent PM and the protective effects depend on the timing of the first dose and the interval between treatments (Nosten and McGready 2015).

7.2.Alternatives to IPTp-SP

7.2.1. Dihydroartemisinin – Piperaquine

A comparison between three doses of IPTp-SP and three doses or monthly dihydroartemisinin – piperaquine (DP) was recently conducted in Uganda (Kakuru et al. 2016). Peripheral blood parasitemia detected by LAMP was significantly higher in the IPTp-SP group than three doses or monthly DP. Similarly, PM (combined active and past infection) was significantly higher among women who received IPTp-SP than women that received three doses or monthly treatment with DP. Although, among primigravid women, the rate of PM was similar between the three groups, the amount of pigment deposition was significantly higher in the IPTp-SP groups, which might indicate higher parasite densities in past infections. The risk of any poor pregnancy outcome (PTD, LBW, congenital anomaly, stillbirth, spontaneous abortion) was significantly lower among women receiving monthly DP than women who received three doses of DP or IPTp-SP.

7.2.2. Mefloquine

In a comparison of IPTp-SP and IPTp-mefloquine (MQ) (Briand et al. 2009), Beninese women received either two doses of IPTp-SP or two doses of MQ (15 mg/kg) during pregnancy. PM was significantly less frequent in the MQ group, but other endpoints including birth weight, LBW, and maternal anemia were similar (Briand et al. 2009). Adverse events were more common with MQ, and overall tolerability was lower (Briand et al. 2009). Another trial compared two doses of IPTp with SP or MQ in women who also received long-lasting insecticide-treated nets. MQ was given as a single 15 mg/kg dose or as a split dose (Gonzalez et al. 2014a). The rates of maternal parasitemia (by BS) at delivery, mild anemia at delivery, and clinical malaria during pregnancy were significantly lower in the MQ group, while PM (by BS or histology), birth weight, and LBW rates were similar (Gonzalez et al. 2014a). As in Benin, tolerability was poor even in the group that received MQ as a split dose (Gonzalez et al. 2014a). IPTp-SP is not recommended for HIV-infected women who take daily cotrimoxazole prophylaxis, owing to the potential adverse effects of taking two antifolate drugs with a common mechanism of action (reviewed in Peters et al. 2007). Two trials evaluated MQ as IPTp in women taking cotrimoxazole (Gonzalez et al. 2014b;). In a multicenter study conducted in East and Southeast Africa, peripheral and placental parasitemia (defined by BS, PCR, or histology) and non-obstetric admission were less frequent among women that received three doses of IPTp-MQ, while maternal anemia, birth weight, and gestational age at delivery were similar between groups (Gonzalez et al. 2014b). Notably, IPTp-MQ was associated with increased mother-to-child transmission of HIV, and again showed poor tolerability (Gonzalez et al. 2014b). In West Africa, IPTp with three MQ doses (15 mg/kg) was compared with cotrimoxazole alone and cotrimoxazole plus IPTp-MQ (Denoeud-Ndam et al. 2014). At delivery, PM was not detected by PCR in any of the 105 women in the cotrimoxazole þ IPTp-MQ group compared with 5/103 women in the cotrimoxazole alone group. Maternal anemia, infection rate during pregnancy detected by PCR, and birth weight did not differ between groups. Again, adverse events were more common among women receiving MQ (DenoeudNdam et al. 2014). Although MQ can be effective to reduce infection, tolerability has been poor even when used at a split dose, and thus may result in low compliance if used for prevention.

7.2.3. Chloroquine – Azithromycin Combination

The CQ – azithromycin combination was compared with SP for use as IPTp in a trial that included six sites in Africa. However, interim analyses showed that the new combination was not superior to the existing intervention, and the study was terminated early (ClinicalTrials .gov Identifier: NCT01103063).

7.3. Intermittent Screening and Treatment

The Intermittent Screening and Treatment in pregnancy (ISTp) strategy entails screening women for malaria infection during antenatal clinic visits using an RDT and treating infection with an antimalarial drug. A multicenter trial comparing ISTp-AL (artemether– lumefantrine) with IPTp-SP was recently conducted in West Africa in sites with seasonal malaria and low SP resistance (Tagbor et al. 2015). PM, birth weight, and maternal hemoglobin were similar between ISTp-AL and IPTp-SP in the overall analysis and within individual sites (Tagbor et al. 2015). Malaria infections between scheduled visits were significantly more frequent in women randomized to the ISTp-AL (Tagbor et al. 2015). In an area of high malaria transmission and high SP resistance in Kenya, women were randomized to three interventions: ISTp with dihydroartemisinin – piperaquine (DP), IPTp with DP, and IPTp-SP (Desai et al. 2015). Malaria infection at delivery was diagnosed by detection of parasites with BS on peripheral or placental blood, or with RDT or PCR on peripheral blood. Risks of malaria infection, mild anemia (HGB, 11 g/dL), stillbirth, and early infant mortality were significantly reduced in women receiving IPTp-DP rather than IPTp-SP or ISTp-DP, while ISTp-DP and IPTp-SP groups did not differ (Desai et al. 2015). The failure of ISTp-DP to improve on IPTp with the failing drug SP echoes the early evaluation of IPTp-SP in 1992 – 1994 (Parise et al. 1998) in which case management was inferior to IPTp-SP.

Differences in ISTp efficacy between the two studies could result from different transmission patterns, being highly seasonal in West Africa versus perennial with seasonal peaks in Kenya. Peripheral parasite density at delivery in Kenya was much lower than the density at enrollment in West Africa. Although the different assessment times could influence BS results, lower parasite densities might explain the lower sensitivity of RDT to detect PM, potentially rendering the IST strategy ineffective in Kenya (Fried et al. 2012; Desai et al. 2015).

7.4.Treatment of Malaria during Pregnancy

Currently, artemisinin combination therapy (ACT) is the first-line treatment for malaria in nonpregnant individuals. Owing to safety concerns, WHO recommends that pregnant women be treated with quinine and clindamycin during the first trimester and with ACT in the second and third trimesters. A multicenter trial reported high cure rate with four different ACTs (artemether– lumefantrine, amodiaquine – artesunate, dihydroartemisinin–piperaquine, and mefloquine –artesunate), with artemether– lumefantrine showing the lowest cure rate of 94.8% (The PREGACT Study Group 2016). Pregnancy outcomes were similar between the four groups and both artemether– lumefantrine and dihydroartemisinin – piperaquine had fewer adverse events than amodiaquine – artesunate, and mefloquine – artesunate (The PREGACT Study Group 2016). Analyses of first-trimester antimalarial treatment records at Shoklo Malaria Research Unit in Thailand have shown that artesunate is as safe as choloroquine and quinine (McGready et al. 2012). In a similar study in Kenya, ACT treatment during the first-trimester (based on the review of treatment records) did not increase the risk of miscarriage, compared with women who did not receive any treatment or women who received quinine (Dellicour et al. 2015). However, community surveillance, which included cases without a treatment record, suggested that exposure to ACT may increase the risk of miscarriage compared with women that never received antimalarial drugs (Dellicour et al. 2015). Because both symptomatic and asymptomatic malaria infections (with P. falciparum or P. vivax) during the first trimester increase the risk of miscarriage (McGready et al. 2012), it might be difficult to assess the contribution attributable to ACT when the comparison group includes never-infected women. Both studies had a small number of women that received either ACT or quinine, and clinical trials to compare the safety of ACT to quinine during the first trimester are needed.[40]

CHAPTER IV: METHODOLOGY

1. STUDY DESIGN

1.1.Type of study

We conducted a prospective study in which we evaluated the parasitological and obstetrical outcomes of IPTp after administration of three doses of Sulfadoxine-pyrimethamine to malaria-free pregnant women from the Jean Zoa Medical Center, Yaounde. Also, we did a cross sectional evaluation of these pregnant women in order to evaluate their sociodemographic and obstetric characteristics.

1.2. Period and duration of study

This study lasted for four months' and ran from February 2024 to May 2024.

1.3.Study site

Our study was conducted at the Jean Zoa medical center, Yaoundé which is in an urban area in the center region of Cameroon where malaria is holoendemic.

2. METHOD OF SAMPLING

All pregnant women with gestational age greater than or equal to 12 weeks of amenorrhea without symptoms and/or signs of malaria and negative blood smear for malaria.

2.1.Inclusion criteria

- Inclusion criteria included pregnant women
- Gestational age greater than 12 weeks of gestation
- A negative blood smears
- Consentment

2.2.Exclusion criteria

- Exclusion criteria included HIV positive pregnant women
- participants with sign and symptoms of malaria infection
- Participants with positive parasitemia
- those less than or equal 12 weeks of gestation

2.3.Size determination

We carried out a consecutive and exhaustive recruitment. The sample size was made of 123 participants.

3. STUDY TOOLS

3.1.Data collection tools.

3.1.1. Physical examination materials

- Thermometer
- Stopwatch
- Medical booklet

3.1.2. Laboratory work up Materials

- RDT
- Blood vials
- Light microscope
- Giemsa stain
- Study medications
    - Sulfadoxine-pyrimethamine

3.2.Procedure

3.2.1. Participants identification and Recruitment

Firstly, we interrogated any pregnant woman visiting the Jean Zoa medical center. We explained to them what the study was about and assessed them for inclusion criteria and eligible pregnant women were enrolled into our study if consented. Secondly, we descended into the community in search for pregnant women and enrollments proceeded as described above.

3.2.2. Data Collection

Data collection forms containing information on the presentation, medical history, physical examination, laboratory results and diagnostic procedures were completed for each participant.

3.2.3. Laboratory technique

Both thick and thin blood smears were taken from enrolled participants and examined for asexual and sexual parasites after staining with 5% Giemsa with a microscope at 100x oil immersion magnification. Blood smears were read by two trained microscopists according to WHO standard procedures. Parasite density discrepancies of > 50% were resolved by averaging of a third microscopist's result and the closer of the two original results.

Parasite density was estimated by counting the number of asexual parasites per 200 leukocytes and multiplying by 40, assuming 8,000 leukocytes/mL.9 Gametocyte density was calculated by counting the number of sexual forms per 1,000 leukocytes and multiplying by eight.11 A Well-structured questionnaire was designed and administered in French and English. However, for all illiterate women, the questionnaire was administered via an interview. The questionnaire sought to obtain demographic data and data on IPTp-SP and INT use.

3.2.4. Follow-up

Slides were prepared on follow-up days 7, 14, 28, 42, 56, 70 and 84 during which the women assessed and tested for malaria. On days 28 and 56, they received their 2nd and 3rd doses of IPTp-SP respectively.

3.3. Study variables or indicators

- Parasitemia
- Fever
- Maternal anemia

4. DATA ANALYSIS

For the prospective study, Descriptive statistics were expressed as means, medians, or proportions. Categorical variables were compared using the chi-squared test and two-sided

Fisher’s exact test, and continuous variables were compared using the Student’s t test or Mann-Whitney test, as appropriate. All statistical analyses were done with IBM SPSS version 29.0.2.0. P values < 0.05 were considered significant. Distribution of parasite clearance rate constants and slope half-lives were generated by the new WWARN Parasite Clearance Estimator.13 Furthermore, when we used the WWARN estimator; all positive parasitemia (by light microscopy) shall be included in the calculations.

For the cross-sectional study, a template of the questionnaire was prepared using Epi Info version 3.4.3 statistical software and the data entered and subsequently exported to the Statistical Package for the Social Sciences SPSS version 29 and analyzed. A descriptive statistical analysis was carried out on the use of INT and IPT. Differences in proportions were analyzed using Chi square tests. A p-value <0.05 was considered to be a statistically significant association.

5. STRENGTHS AND WEAKNESSES OF THE STUDY

The limitations and strengths of this study will be known at the end.

6. ETHNICAL CONSIDERATION

As stipulated by the WHO guidelines for clinical practice, once finished, our protocol and questionnaire form were submitted to the Ethical Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I and the National Committee for ethical evaluation and approval. Authorization from the directors of study sites, the heads of the various units concerned.

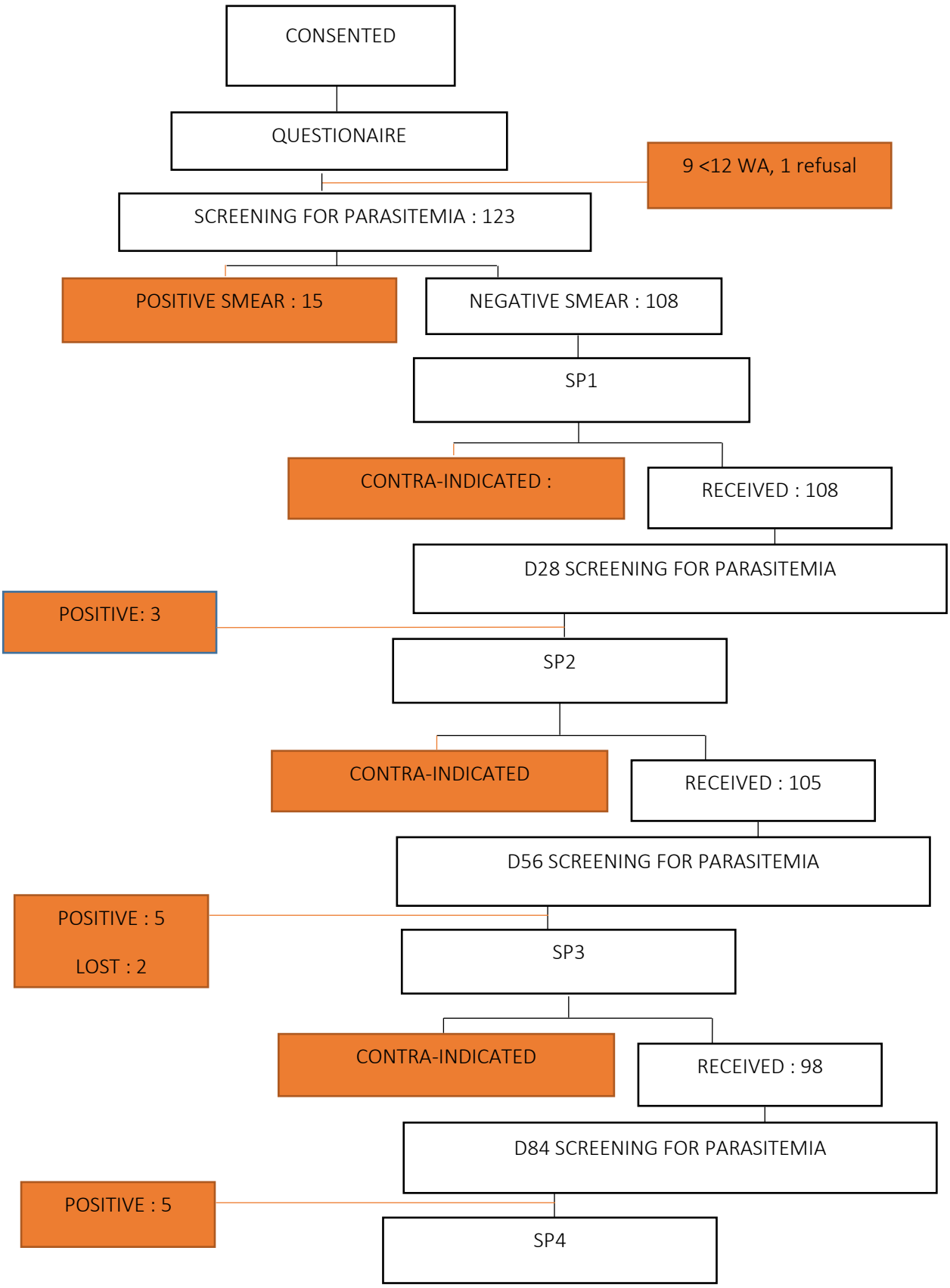

Figure 3: Sampling and follow-up Flow chart

CHAPTER V: RESULTS

1. SCREENING OF POPULATION

1.1. Consent:

Out of the 133 women interviewed on day 0 for this study, 25 were considered ineligible.

1.2. Reasons for ineligibility :

15 of the 25 had a positive parasitaemia, 1 refused consent while 9 had a gestational age of less than 12 weeks.

1.3. Prevalence of Malaria amongst screened subjects

Twenty-eight (22.8%) of the screened population had positive malaria parasite test results, amongst which, 23 (82%) had a positive RDTs and 5 tested positive on microscopy.

Table I: Prevalence of malaria in screened population

		Thick smear results		
		Positive (%)	**Negative (%)**	**Total**
RDT	**Positive**	23 (100)	0 (0)	23
	Negative	5(5.0)	95 (95.0)	100
	TOTAL	28 (22.8)	95 (77.2)	123

2. SOCIO-DEMOGRAPHIC DATA

2.1.Socio-demographic characteristics of screened subjects

One hundred and twenty-three pregnant women were screened for malaria and responded to a questionnaire on demographic information, previous use of malaria medications and malaria prevention practices.

The mean age of the respondents was 28.4 ± 5.14 years, with an age range from 21 to 41 years. 74 (60.2%) of the respondents were single while 49 (39.8%) where married. 15 (12.2%) of the respondents were housewives, 34 (27.6%) where businesswomen, 15 (12.2%) were civil servants, 30 (24.4%) did vocational jobs, 20 (16.3%) were students while 9 (7.3%) did other jobs.

Table II: Socio-demographic characteristic of study participants

Characteristic	Number(n)	Percentage (%)
Age		
≤25	41	33.3
26-34	62	50.4
≥35	20	16.3
Marital status		
Married	49	39.8
Single	74	60.2
Employment status		
Business	34	27.6
Civil servant	15	12.2
Housewife	15	12.2
Vocational	30	24.4
Students	20	16.3
Others	9	7.3
Total	123	100

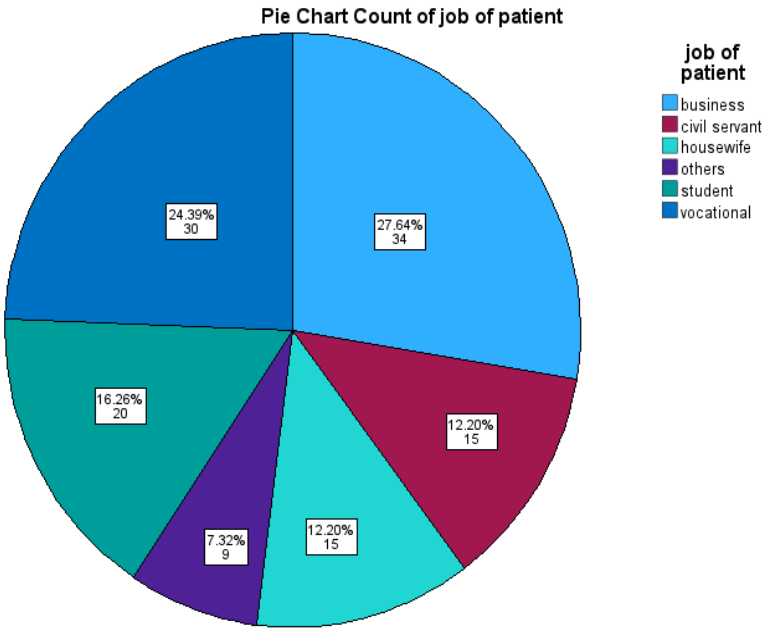

Figure 4: Distribution of study participants with respect to employment status

2.2.Prevalence of Malaria in relationship with socio-demographic factors in screened population

12 (29.3%) of the respondents who were ≤25 years old of age tested positive for malaria compared to 2(15%) in those ≥35 years old. The association between malaria test results and respondents age was statistically significant (p=0.023). Marital status was not significantly associated with malaria test results.

Table III: The association between socio-demographic factors and malaria prevalence

Characteristic	Malaria status		Statistical test	P-value
	Positive n(%)	Negative n(%)		
Age in years				
≤25	12 (29.3%)	29 (70.7%)		
26-34	14 (24.2%)	48 (75.8%)	9.804	0.023
≥35	2 (15%)	18 (85%)		
Employment status				
Businesswomen	7 (20.6)	27 (79.4)		
Housewife	4 (26.7)	11 (73.3)		
Students	5 (25.0)	15 (75.0)	8.322	0.044
Vocational	7(23.3)	23 (76.7)		
Civil servants	2 (13.3)	13 (86.7)		
Others	3 (33.3)	6 (66.7)		
Marital status				
married	11 (22.4)	38 (77.6)		0.983
Single	17 (30.0)	57 (70.0)		
Total	28	95		

3. Past Medical History

3.1.General Medical history :

3(2.4%) of our study participants have a history of urinary tract infection while 2(1.6%) have history of vaginitis.

Table IV: **Medical History of screened population**

Characteristics	Frequency(n)	Percent(%)
Urinary tract infections	3	2.4
Vaginitis	2	1.6
Total	5	4

3.2. Obstetrical data

3.2.1. Obstetric characteristics of screened subjects

On enrollement, the mean gestational age was 20weeks, ranging from 12 to 36weeks. 97 (78.9%) were in their second trimester, 15 (12.2%) were in their third trimester while 11(8.9%) where in their first trimester.

Multigravidae made up 69 (56.1%) followed by Secundigravidae at 30 (24.4%) and primigravidae were the minority at 24 (19.5%). The mean parity of our study population was 1.84 children ranging from 0 to 7.

Table V: Age and gestational age of study participants

	Mean	Range
Parity	1.84±1.6	0-7
Age of Pregnancy(weeks)	20 ±6	12-36 wks

Table VI: **Gestational age and trimester distribution of screened subjects**

Characteristics	Frequency(n=123)	Percentage (100%)
Parity		
Prim gravidae	24	19.5
Secundigravidae	30	24.4
Multigravidae	69	56.1
Trimester		
1st trimester	11	8.9
2nd trimester	97	78.9
3rd trimester	15	12.2
ANC Visit		
< 4th ANC	105	85.4
≥ 4th ANC	18	14.6
Total	123	100

3.2.2. Prevalence of malaria in relationship with Obstetric characteristics in screened population

Positive test results for malaria were found in three (27.3%) of the examined population in the first trimester, seventeen (17.5) in the second trimester, and eight (53.3%) in the third trimester. Positive test findings for malaria were obtained from 10 (41.7%) primigravidae, 8 (26.7%) secundigravidae, and 10 (14.5%) multigravidae. 28 (28.6%) of those who did not attain the required 4 or more ANC tested positive for malaria while none of those that attended the required 4 or more ANC tested positive for malaria. There was a statistically significant relationship between the number of ANC (P-Value=0.01), parity (p-value=0.04) and trimester (0.002) with malaria prevalence.

Table VII: The relationship between malaria prevalence with obstetric characteristic

Characteristic	Malaria status		Statistical test	P-value
	Positive n(%)	Negative n(%)		
Trimester				
1st Trimester	3 (27.3)	8 (72.7)	12.154	0.002
2nd Trimester	17(17.5)	80(82.5)		
3rd Trimester	8 (53.3)	7 (46.7)		
Parity				
Primigravidae	10 (41.7)	14 (58.3)	7.067	0.029
secundigravidae	8 (26.7)	22 (73.3)		
Multigravidae	10 (14.5)	59 (85.5)		
Number of ANC				
< 4 ANC	28 (28.6)	77 (71.4)	6.802	0.009
≥4 ANC	0 (0.0)	18 (100)		

3.3. Past history of Malaria prevention

3.3.1. Malaria prevention practices of screened subjects.

87 (70.7%) of our study population used ITN. 67.5% (83) used residue indoor spraying. There was a statistically significant relationship(P=0.001) between the number of antenatal consultations and the number of IPTp-SP doses received

Table VIII: Malaria preventive practices

	Frequency(n)	Percentage (%)
Usage of ITN	87	70.7
Indoor Residual Spraying	83	67.5
TOTAL	123	100

Table IX : Relationship between number of ANC's and IPTp-SP doses

Number of ANC visits	Doses[n(%)]			Test statistic	P value
	≤1	2	≥3		
<4	17(20.2)	29(34.5)	38(45.2%)		
≥4	0	1(9.1)	10(90.9)	15.261	0.001

3.3.2. Prevalence of malaria and relationship with Malaria Prevention practices

Ten (10.5%) of the participants who had taken at least one dose of IPTp-SP tested positive for malaria. The association between malaria test results and uptake of IPTp-SP was statistically significant (P=0.00005). No significant association between usage of ITN (P=0.75) and indoor residue spraying (P=0.051).

Table X: Association between malaria prevalence and IPTp-SP

	Positive parasitaemia (%)	**Negative parasitaemia (%)**	**Odd ratio**	**P value**
IPTp SP yes	10 (10.5)	85 (89.5)	0.0631	0.00005
IPTp SP no	18 (64.3)	10 (35.7)		
Total	28 (22.8)	95 (77.2)		

Table XI: Association between malaria prevalence and ITNs

	Positive parasitaemia (%)	**Negative parasitaemia (%)**	**Odd ratio**	**P value**
Usage of ITNS	17 (19.5)	70 (80.5)	0.522	0.137
Non usage of ITNs	11 (30.5)	25 (69.5)		
Total	28 (22.8)	95 (77.2)		

Table XII: Association between malaria prevalence and IRS

	Positive parasitaemia (%)	Negative Parasitaemia (%)	Odd ratio	P value
IRS yes	15 (18.1)	68 (81.9)	0.443	0.057
IRS no	13 (32.5)	27 (67.5)		
Total	28 (22.8)	95 (77.2)		

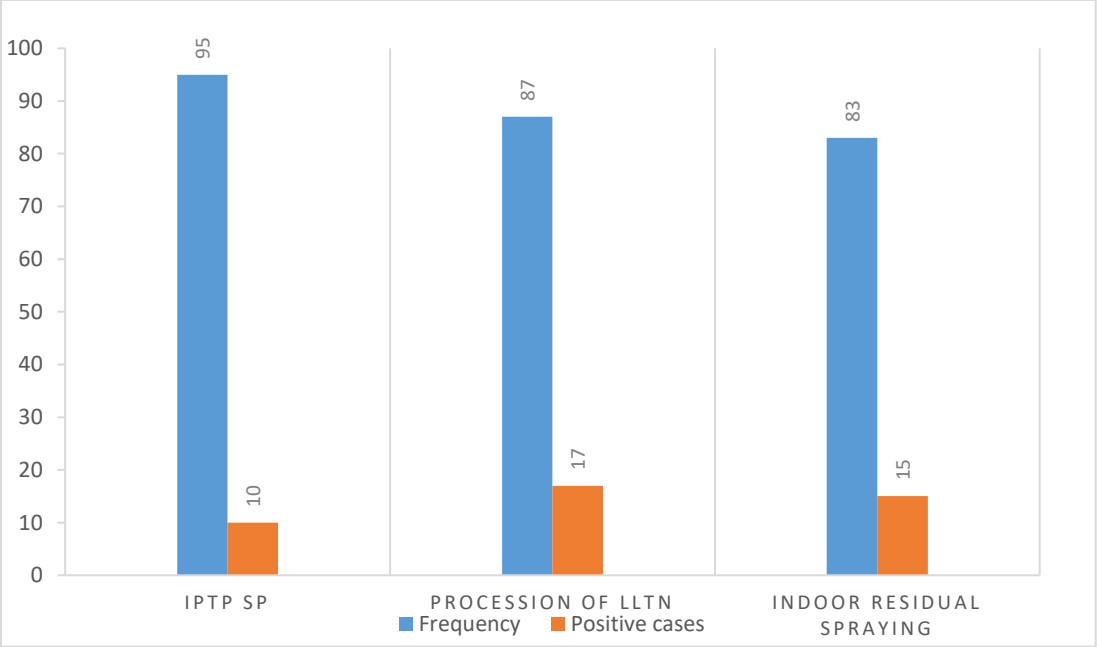

Figure 5: Malaria prevention practices in relationship with malaria prevalence

3.4. Medication History

3.4.1. Medical and anti-malarial drug history of screened subjects

Thirteen (10.5%) of the participants used anti-malaria drugs in the previous months, amongst which 8 (61.5%) used IV artesunate, 3 (23.1%) used IV quinine and 2 (15.4%) used other treatments.

Table XIII: Antimalaria drug used during pregnancy

		Number(N)	Proportion (%)
Fever within previous month		00	
History of use of anti-malaria drug within previous month	Yes	13	10.5
	IV artesunate	8	6.5
	IV Quinine	3	2.4
	Others	2	1.6
	No	110	89.5

3.4.2. Other Medications

110(89.4%) of our participants were on folic acid, 99(80.5%) were on iron supplement and only 63(51.1%) were on calcium supplement.

Table XIV: Antenatal visits and care

		Number(N)	Proportion (%)
Folic acid supplement	Yes	110	89.4
	No	13	10.6
	Unknown	0	0
Iron supplement	Yes	99	80.5
	No	24	19.5
	Unknown	0	0
Calcium supplement	Yes	63	51.1
	No	60	48.9
	Unknown	0	0

4. Participant follow up

4.1. Compliance to follow-up

As per follow-up, 108 (87.8%), 105 (85.4%), 98 (79.7%) were re-evaluated on days 28, day 56 and 84 respectively as presented in figure 6 and flow-chart below

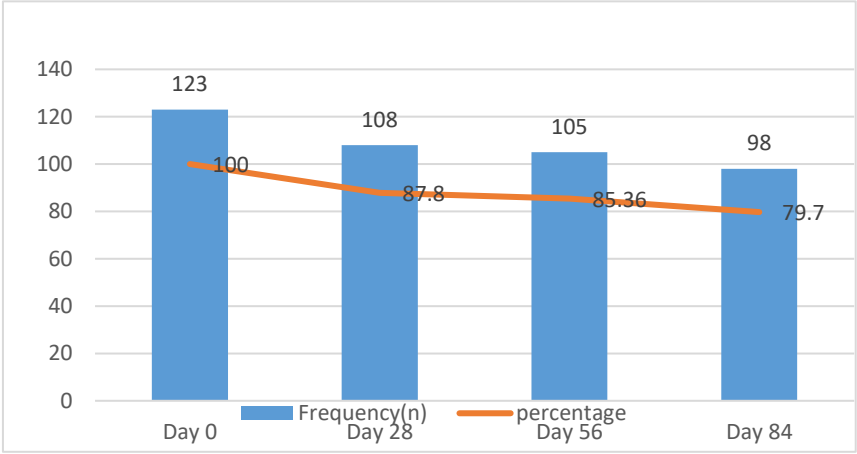

Figure 6: Follow-up participation

4.2. Loss to follow up:

During follow-up, those that tested positive were terminated and there were 2 lost to follow-up as shown in the flow chart below.

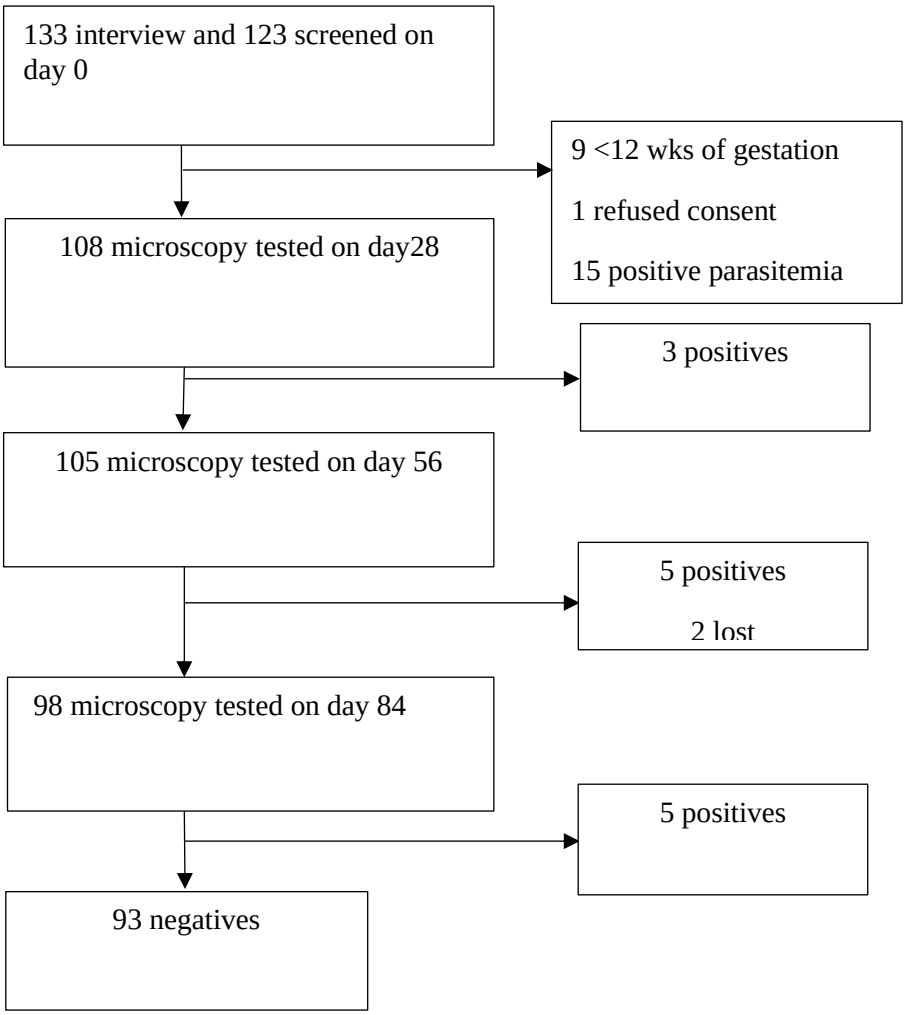

Figure 7: Follow-up flow diagram for efficacy study of IPTp based on SP

4.3. IPTp administration during follow-up

77.3% (95) of the women took the IPTp-SP. Among the women who took IPTp-SP, the complete coverage of the adequate SP dosage (3 doses or more of SP) was 50.5% (48) while 17.9% (17) received 1 dose, respectively. The prevalence of ≥ 2 doses were 84.5% (104).

Table XV: IPTp administration during follow up

	Number(n)	Percentage (%)
IPTp-SP (3 doses)	48	50.5
IPTp-SP (2 doses)	30	31.6
IPTp-SP (1 dose)	17	17.9
Total	95	100

On each follow up day, each woman was given 3 tablets of SP as DOT. 95 received it under directly observation while 28 returned home with their SP

Table XVI: **Follow up and screened subjects who didn't receive their under direct observation**

	Day 28	**Day 56**	**Day 84**	**Total**
IPT 1	5	2	0	7
IPT 2	4	3	2	9
IPT 3	3	5	4	12
Total	12	10	6	28

4.4. Parasitological outcomes

Of the 108 women who attended the day 28 visit post-treatment, 3 had a positive parasitaemia giving us an incidence of malaria of 2.8%, On day 56, 105 were screened and we had 05 who had a positive parasitaemia given us an incidence of malaria of 4.8% and finally 98 women were screened on day 84 as two were lost, 5 had a positive parasitaemia giving us an incidence of malaria of 5.1%. The overall prophylactic failure in our study was 12.0%.

Table XVII: Incidence of malaria infection during follow-up

	Thick film Positive, n (%)	**Cumulative Positivity**	**Cumulative Positivity rate(thick film)**	**Cumulative negativity rate(thick film)**
Day 28	3 (2.8)	3	2.8	97.2
Day 56	5 (4.8)	8	7.4	92.6
Day 84	5 (5.1)	13	12.0	88.0

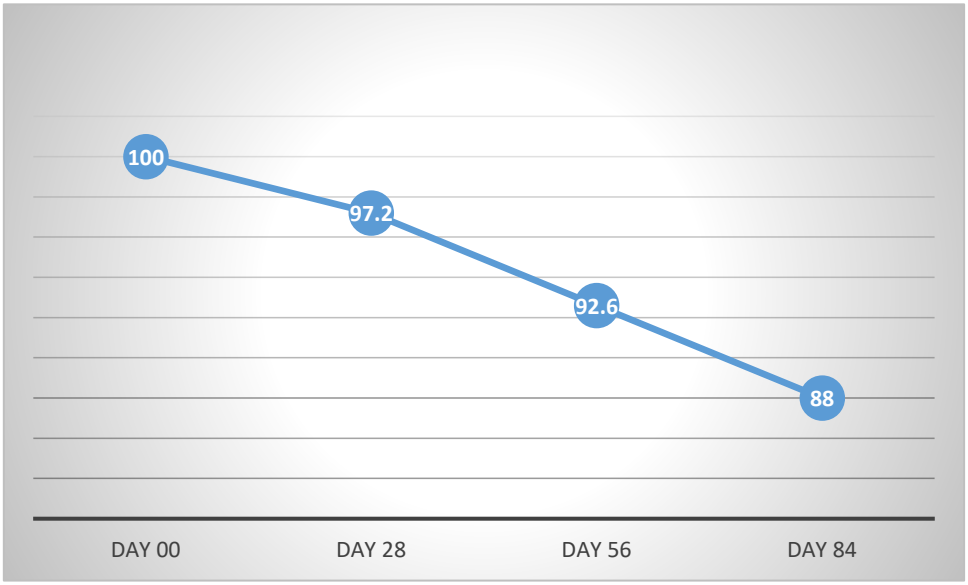

Figure 8: Cumulative negative rate

4.5. Obstetrical adverse outcomes.

No obstetrical adverse outcomes were noted

4.6. Observed Adverse events

In this study, no adverse event was recorded. No threatened nor abortion registered during follow-up.

CHAPTER VI : DISCUSSIONS

Malaria prevention in pregnancy with IPTp-SP is one the strategies recommended by WHO in Sub-Saharan African were MiP related morbidity and mortality is pronounced. Growing concerns about the waning efficacy of IPT-SP is threatened by rising levels of parasite resistance to SP in several countries across Africa. This is due to emergence and successive acquisition of polymorphism in both the P. falciparum dihydrofolate reductase/dihydropteroate synthetase(pfdhfr/pfdhps) genes, observed to be associated with treatment failure in several epidemiological settings. In this study, aimed to determine the parasitological efficacy and safety of IPTp-SP in the Jean Zoa Medical center.

IPTp-SP Coverage and ITN Ownership and usage

All of the women were prescribed IPTp-SP during pregnancy and 50.5% received the recommended three or more doses of IPTp-SP which is higher than the 29.3% from the National demographic health survey (DHS) data collected in 2011 in Cameroon [56] and 29.5% obtained from malaria indicators surveys conducted in Burkina Faso, Ghana, Mali, Malawi, Kenya, Nigeria, Sierra Leone and Uganda. [58].

Comparatively, the coverage of IPTp-SP 3 or more doses in the Jean Zoa Medical Center appears to be higher than many other countries in the Sub-Saharan Africa except for Ghana where a similar but slightly higher coverage of 60% has been reported.[59] Also, a similar coverage of 47.0% was reported in the mount Cameroon region.[5] The relatively higher uptake of SP at the hospital may be due to stock availability, primarily because the hospital is located in an urban area making access to new stocks easier compared to rural health facilities where periodic shortage has been reported as a major barrier to the implementation of IPTp-SP program in some malaria endemic countries. Also, proper health education given at ANC visits help to create awareness for the women who will be more likely to request for IPTp.

The overall usage rate of ITN obtained from the study was 70.7%, which was similar to that reported by Gontie et al in the sherkole district, west Ethiopia[9] , but higher than 43.0% reported by Leonard et al in Cameroon 2016.[3]This might be due to the free distribution of ITN and the multiple health promotion messages received during ANC on the dangers of malaria and the importance of ITN . Although this indicates that the target has been reached, more studies need to be done.

Prevalence of malaria in our study participants

This study observed a high prevalence of malaria parasitemia among pregnant women during their ANC visit in Jean Zoa Medical Center. The malaria parasitemia prevalence in this study population was 22.8%. The prevalence of parasitemia seen in the study is comparable to those reported elsewhere in Cameroon: 22.4% in Mount Cameroon[60] and in Africa: the middle belt of Ghana (20.3%)[1]. This result was lower than those obtained in Gombe, North Eastern Nigeria.[6] by Ali and collaborators. This difference may be due to better implementation of improved malaria interventions including increased coverage in the distribution of ITNs, which showed that 70.9% of our respondent utilize ITN. Furthermore, there was a significant association (<0.05) between malaria prevalence and IPTp-SP. Therefore, these interventions might reduce the burden in the study area.

Overall, malaria prevalence decreased with increasing age, parity and number of ANC visits. This reinforces the suggestion that the ability to control malaria parasitemia is parity and age dependent. Also, through regular participation in antenatal care, women gain adequate knowledge about the dangers of malaria during pregnancy and subsequently improve their attitudes and practices regarding prevention of MiP.

Prevalence of malaria during follow-up.

Overall, 12.0% of pregnant women in the study experienced prophylactic failure of SP throughout the 84 days follow-up. This observation was similar to that made by Chapanda et al in Zambia, 2021.[61] It is difficult to establish the precise prophylactic failure rate because it is unknown how many women who tested negative by microscopy at day 0 may have later been exposed to malaria infection post-treatment. This is because some women may have become infected after receiving IPTp-SP, cleared the parasitemia to reflect important prophylactic effect but were indistinguishable from other women who may have never been exposed to the parasite. Nonetheless, calculating the prophylactic failure based on the number of positive women from those who tested negative at day 0 is a reasonable and proxy estimate of true prophylactic failure, especially in endemic areas.

Study limitation :

- Although SP was given as directly observed treatment (DOT), to ensure that pregnant women take the full dose, assessment of the reliability of IPTp-SP

uptake is by evaluating the presence of measurable sulfa in the maternal plasma during pregnancy.

- Due to time-limitations, Follow-up period could not be extended to include post-natal period
- Because of logistic reasons, more sensitive malaria diagnostic tools such as PCR methods were not available to detection very low parasitemia malaria which otherwise could not be detected by microcopy and RDT

CONCLUSION

At the end of this study which had as objective, to document the efficacy and safety of IPTp-SP in Jean Zoa Medical Center, Yaounde;

- Use of IPTp based on SP is associated with lower rate of malaria parasitemia during pregnancy
- IPTp based on SP was effective in preventing malaria in 77.2% of pregnant women
- No Adverse medical and obstetrical outcome was associated with the use of SP for IPT as observed in the study population

RECOMMENDATIONS

- **To researchers**
  - Carry out similar study on a larger sample size
  - Extend follow-up period to include post-natal period
  - Carry out study on molecular markers of SP resistance
- **To The Ministry of Public Health**
  - To organize or provide opportunities and training sessions to create awareness on IPTp guidelines.
  - Ensure a constant supply of SP to the hospital so as to avoid stock outs.
- **To the Health Facilities**
  - They should ensure a constant supply of water and cups on ANC days.
  - Intensify health talks on ANC days in order to educate pregnant women on the need of malaria preventive strategies during pregnancy.
- **To Pregnant women**
  - Start ANC early so as to receive the recommended three or more doses of IPTp-SP.

REFERENCES

1. Dosoo DK, Chandramohan D, Atibilla D, et al (2020) Epidemiology of malaria among pregnant women during their first antenatal clinic visit in the middle belt of Ghana: a cross sectional study. Malar J. https://doi.org/10.1186/s12936-020-03457-5

2. world malaria report 2020_.pdf.

3. Leonard N, Eric FB, Judith A-KK, Samuel W (2016) Factors associated to the use of insecticide treated nets and intermittent preventive treatment for malaria control during pregnancy in Cameroon. Arch Public Health 74:5

4. Hill et al. - 2013 - Factors Affecting the Delivery, Access, and Use of.pdf.

5. Anchang-Kimbi JK, Kalaji LN, Mbacham HF, Wepnje GB, Apinjoh TO, Ngole Sumbele IU, Dionne-Odom J, Tita ATN, Achidi EA (2020) Coverage and effectiveness of intermittent preventive treatment in pregnancy with sulfadoxine–pyrimethamine (IPTp-SP) on adverse pregnancy outcomes in the Mount Cameroon area, South West Cameroon. Malar J. https://doi.org/10.1186/s12936-020-03155-2

6. Ali R (2022) Malaria Prevalence among Pregnant Women in Relation to Parity, Gestation Period and Age in Gombe, North Eastern Nigeria. J Appl Sci Environ Manag 26:1063–1066

7. Almaw A, Yimer M, Alemu M, Tegegne B (2022) Prevalence of malaria and associated factors among symptomatic pregnant women attending antenatal care at three health centers in north-west Ethiopia. PLOS ONE 17:e0266477

8. Cn K, Vo O (2022) Prevalence and Risk Factors of Malaria among Pregnant Women receiving Antenatal Care in a Health Facility in Delta State, Southern Nigeria. J Health Med Sci. https://doi.org/10.31014/aior.1994.05.03.233

9. Gontie GB, Wolde HF, Baraki AG (2020) Prevalence and associated factors of malaria among pregnant women in Sherkole district, Benishangul Gumuz regional state, West Ethiopia. BMC Infect Dis 20:573

10. Boel ME, Rijken MJ, Brabin BJ, Nosten F, McGready R. The epidemiology of postpartum malaria: a systematic review. Malar J 2012; 11: 11m ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodefciency virus type 1 and malaria in pregnant women in sub-saharan Africa. Am J Trop Med Hyg 2004; 71 (suppl 2): 41–54.

11. ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodefciency virus type 1 and malaria in pregnant women in sub-saharan Africa. Am J Trop Med Hyg 2004; 71 (suppl 2): 41–54.

12. Steketee RWNB, Parise MEMC. The burden of malaria in pregnancy in malaria-endemic areas. Am J Trop Med Hyg. 2001;64:28–35.

13. BJ B. An analysis of malaria in pregnancy in Africa. Bull World Health Organ 1983; 61:1005–1016.

15. WHO. A Strategic Framework for Malaria Prevention and Control During Pregnancy in the African Region, In World Health Organization RegionalOffice for Africa. AFR/MAL/04/01. 2004.

16. Service EMW, Forest N. The Encyclopedia of Arthropod-Transmitted Infections. 2002;324(February).

17. White GB, Faust C. Appendix 4 - Medical Acarology and Entomology *Internet+. Twenty Thi. Manson's Tropical Diseases. 1258-1272.e2 p. Available from: http://dx.doi.org/10.1016/B978-0-7020-5101- 2.00088-1.

18. Hay SI, Sinka ME, Okara RM, Kabaria CW, Mbithi PM, Carolynn C, et al. Developing Global Maps of the Dominant Anopheles Vectors of Human Malaria. 2010;7(2):1–6.

19. Stauffer WM, Konop RJ, Kamat D. Traveling with Infants and Young Children Part I : Anticipatory Guidance : Travel Preparation and Preventive Health Advice.

20. Autino B, Noris A, Russo R, Castelli F. Epidemiology of Malaria in Endemic Areas. 2012;

21. Remember malaria , even after a year Generous prescribing advised for travelling to areas of drug shortage. 1995;311:1995.

22. Ghebreyesus TA, Haile M, Witten KH, Getachew A, Yohannes AM, Yohannes M, et al. northern Ethiopia : community based incidence survey. 1999;663–6.

23. Hviid L, Duffy PE, Leke RFG, Taylor DW. Malaria in pregnancy: pathogenesis and immunity. Lancet Infect Dis. 2007; 7: 105-117.

24. keogh bararrack, Ash Vale A. surgeon-major Ronald Ross,IMS Nobel laureate in medicine for his work on malaria. 2015;

25. Eisen RJ, Schall JJ. Life history of a malaria parasite (Plasmodium mexicanum): independent traits and basis for variation. 2000(January).

26. Ejigiri I, Sinnis P. Plasmodium sporozoite – host interactions from the dermis to the hepatocyte.

27. Sakmann B, Hausser M. Migration of Plasmodium Sporozoites Through Cells. 2001;261(January).

28. Markus MB. Malaria : Origin of the Term '" Hypnozoite ."' 2011;781–6.

29. Oh SS. Two Plasmodium falciparum merozoite proteins binding to erythrocyte band 3 form a direct complex. 2005;338:1690–5.

30. Horuk R, Chitnis CE, Darbonne WC, Colby TJ, Rybicki A, Hadley TJ, et al. A Receptor for the Malarial Parasite Plasmodium vivax : The Erythrocyte Chemokine Receptor. 1993;8(2):6–8.

31. Bannister LH, Hopkins JM, Fowler RE, Krishna S, Mitchell GH. A Brief Illustrated Guide to the Ultrastructure of Plasmodium falciparum Asexual Blood Stages. 2000;4758(1998):427–33.

32. Przyborski J, Lanzer M, Viebig NK, Gamain B, Scheidig C, Le C, et al. Asinglememberofthe Plasmodium falciparum var multigene family determines cytoadhesion to the placental receptor chondroitin sulphate A. 2005;6(8).

33. Adams S, Brown H, Turner G. Breaking down the blood – brain barrier : signaling a path to cerebral malaria ? 2002;18(8):360–6.

34. Bannister L, Mitchell G. The ins , outs and roundabouts of malaria. 2003;19(5):209–13.

35. Cowman AF, Crabb BS. Review Invasion of Red Blood Cells by Malaria Parasites. 2006;755–66.

36. Prato M, Khadjavi A, Mandili G. Insecticides as Strategic Weapons for Malaria Vector Control. 2008.

37. Aly ASI, Vaughan AM, Kappe SHI. Malaria Parasite Development in the Mosquito and Infection of the Mammalian Host.

38. Fried M, Duffy PE (2017) Malaria during Pregnancy. Cold Spring Harb Perspect Med 7:a025551

39. Takem EN, D'Alessandro U (2013) MALARIA IN PREGNANCY. Mediterr J Hematol Infect Dis 5:e2013010

40. Molyneux ME. Malaria - clinical features in children. 1989;82(17):35–8.

41. Szmitko PE, Kohn ML, Simor AE. Plasmodium falciparum malaria occurring 8 years after leaving an endemic area. Diagn Microbiol Infect Dis [Internet]. 2009;63(1):105–7. Available from: http://dx.doi.org/10.1016/j.diagmicrobio.2008.08.017.

42. Malaria C. Cerebral malaria : clinical featu res , pathophysiology and treatment. 1997;91(7).

43. Meibalan E, Marti M. Biology of Malaria Transmission. 2017;1–15.

44. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Europe PMC Funders Group Vivax malaria : neglected and not benign. 2009;77(61):79–87.

45. Thomas G, Company WBS, Mackie CTT, Hunter MGW, Brooke CC, Worth A. Hunter's Tropical Medicine and emerging infectious diseases. 2001;43(2):7216.

46. singh B, Sung LK, Matusop A, Radhakrishnan A, Shamsul SSG, Cox-singh J, et al. A large focus of naturally acquired Plasmodium knowlesi infections in human beings. 2004;363:1017–24.

47. Harold W. Brown M. Malaria parasites and other haemosporidia. 2015;2015.

48. DAVID A. WARRELL, D.M. SL. dexamethasone proves deleterious in cerebral malaria. 1982.

49. Beare NA, Southern C, Chalira C, Taylor TE, Molyneux ME, Harding SP. Prognostic Significance and Course of Retinopathy in Children With Severe Malaria. 2004;122.

50. Whitty JM, Chiodini PL. UK Malaria Treatment Guidelines. J Infect [Internet]. 2016; Available from: http://dx.doi.org/10.1016/j.jinf.2016.02.001.

51. White NJ. Anaemia and malaria. Malar J [Internet]. 2018;1–17. Available from: https://doi.org/10.1186/s12936-018-2509-9.

52. Carter JA, Neville BGR, White S, Ross AJ, Otieno G, Mturi N, et al. Increased Prevalence of Epilepsy Associated with Severe Falciparum Malaria in Children. 2004;45(8):978–81.

53. Brabin BJ, Bates I, Cuevas LE, Haan RJ De, Ph D, Phiri AI, et al. Severe Anemia in Malawian Children. 2008;

54. Health I, Malaria RB. Severe Malaria. 2014;19:7–131.

55. Makris K, Spanou L. Acute Kidney Injury : Definition , Pathophysiology and Clinical Phenotypes. 2016;37(2):85–98.

56. Dionne-Odom J, Westfall AO, Apinjoh TO, Anchang-Kimbi J, Achidi EA, Tita ATN (2017) Predictors of the use of interventions to prevent malaria in pregnancy in Cameroon. Malar J. https://doi.org/10.1186/s12936-017-1786-z

57. World Health Organization - 2020 .pdf.

58. Yaya S, Uthman O, Amouzou A, Bishwajit G (2018) Use of Intermittent Preventive Treatment among Pregnant Women in Sub-Saharan Africa: Evidence from Malaria Indicator Surveys. Trop Med Infect Dis 3:18

59. Owusu-Boateng and Anto - 2017 - Intermittent preventive treatment of malaria in pr.pdf.

60. Anchang-Kimbi JK, Nkweti VN, Ntonifor HN, Apinjoh TO, Tata RB, Chi HF, Achidi EA (2015) Plasmodium falciparum parasitaemia and malaria among pregnant women at first clinic visit in the mount Cameroon Area. BMC Infect Dis. https://doi.org/10.1186/s12879-015-1211-6

61. Enesia Banda Chaponda RMC (2021) Sulfadoxine-pyrimethamine parasitological efficacy against Plasmodium falciparum among pregnant women and molecular markers of resistance in Zambia: an observational cohort study. Malar J 10

APPENDIX

APPENDIX 1

Data collecData collection form

Parasitemia and obstetric outcome of intermittent preventive treatment of malaria In pregnancy.

CASE REPORT FORM

1. **IDENTIFICATION**

CODE D'IDENTIFICATION:			**…..**		
Noms et prénoms :	**……**		**Statues Matrimonial:**		☐ Mariée ☐ Non-Mariée
Date de naissance:	……../……/…… *Jour / mois / Année.*		**Age :**		…… / …… *An / mois*
Domicile:	**……**	**Ethnie :**	**……**	**Tel. :**	**……..**
Occupation:	**……..**				

2. **Eligibilité**

3.3.Critères d'inclusion

Pregnant :	☐Yes/ ☐No
GE	☐(+ve)/ ☐(-ve) ***if (+VE) , Parasitemia*** …….. ***/µl)***:
RDT	☐Yes/ ☐No

2.2. Critères d'exclusion

			Observations
Domicile			
Signes de paludisme simple et grave	Convulsion:	☐Yes/ ☐No	
	Anemie severe:	☐Yes/ ☐No	
	Vomissements persistantes ou non:	☐Yes/ ☐No	
	Incapacité à boire ou à manger :	☐Yes/ ☐No	
Grossesse à risque :		☐Yes/ ☐No	
Symptômes Obstétricaux *(contractions utérines, ou Saignements vaginales etc)* :		☐Yes/ ☐No	
Antécédent d'allergie au médicament d'étude :		☐Yes/ ☐No	
Refus de participer :		☐Yes/ ☐No	

Date de Recrutement :	……/……./…..…. *Jour / mois /Année.*	Lieu de Recrutement :	**…….……**
Profile du Lieu :	☐Formation Sanitaire ☐Ménage ☐ Autre **:……**		

3. SYMPTOMES (J0)

		Observations
Asthénie ?	☐Yes/ ☐No	
Vertiges ?	☐Yes/ ☐No	
Nausées ?	☐Yes/ ☐No	
Vomissements ?	☐Yes/ ☐No	
Toux ?	☐Yes/ ☐No	
Dyspnées ?	☐Yes/ ☐No	
Anorexie ?	☐Yes/ ☐No	
Douleurs abdominales ?	☐Yes/ ☐No	
Diarrhée ?	☐Yes/ ☐No	
Eruption cutanées ?	☐Yes/ ☐No	
Dysurie ?	☐Yes/ ☐No	
Leucorrhées ?	☐Yes/ ☐No	
Saignements vaginaux ?	☐Yes/ ☐No	
Dyspareunie ?	☐Yes/ ☐No	
Autres symptômes ?	☐Yes/ ☐No	*Citez-le : ……*

4. ANTECEDENTS GYNECO-OBSTETRIQUES

Gravida:	**….**	Parité :	**…./ …./ …./ …./**	**DDR**:	……../…./….. *Jour / mois /An.*	Age de la Grossesse : (sem)	**…….**
Gpe Sang. ABO:		**…….**	Gpe Sang.RH :	**…….**	Electroph. Hgb:	**…….**	
Nombre de Doses de TPI (S/P) depuis de début de la grossesse ?							
Date de la dernière dose ?						**……. ,……/……/**	
Utilisation de MILDA?						☐Yes/ ☐No	
Pulvérisation ?						☐Yes/ ☐No	
Nombre de doses de Td ?						**…….**	

4.1. Maladies pendant la grossesse en cours ? Oui/non

Si oui,

	Maladie 1	Maladie 2	Maladie 3
Symptoms			
Diagnostic			
Treatement			

5. ANTECEDENTS MEDICAUX

Maladies infectieuses chroniques :	☐Yes/ ☐No	Citez-le (s) : ……
Autres Maladies chroniques :	☐Yes/ ☐No	Citez-le (s) : ……..
Immuno-allergiques :	☐Yes/ ☐No	Citez-le (s) : ……..
Fièvre (moins d'un mois avant ce jour):	☐Yes/ ☐No	

5.1. ATCD Médicamenteux:

		Sp1	**Sp2**	**Sp3**
Sulfadoxine-pyrimethamine(sp)	Date :	…../…./ …... *Jr /mois /An.*	…../…./ …... *Jr /mois /An.*	…../…./…... *Jr /mois /An.*
Autres				

Autres Traitement en cours :	Fer?	☐Yes ☐No	Acide Folique?	☐Yes/ ☐No
	Autre (1)?	☐Yes ☐No **……..**	Autre (2)?	☐Yes ☐No **……..**

6. EXAMEN PHYSIQUE (J0) :

6.1. Examen General

			Observations
Température :	……^{o}C)		
Poids (kg):	…….. Kg		
Fréq. Card. :	……../mins:		
Conjonctives :	Pâleurs?	☐Yes/ ☐No	
Autres			

6.2. Examen Systémique

Poumons :	Râles Bronchiques ?	☐Yes/ ☐No	
	Râles Crépitant ?	☐Yes/ ☐No	
Cœur :	Souffles cardiaq.?	☐Yes/ ☐No	
	Autres : ……		
Abdomen (Palpations):	Douleurs abdomens?	☐Yes/ ☐No	
	Hépatomégalie?	☐Yes/ ☐No	
	Splénomégalie?	☐Yes/ ☐No	
Autres signes cliniques:	*Citez-le(s) :* ……		

6.3. Examens obstétricaux

BDCF (/mins):	…….	MAF?	☐Yes/ ☐No	Contractions Utérines ?	☐Yes/ ☐No
Saignement Vag. ?	☐Yes/ ☐No	Leucorrhées	☐Yes/ ☐No	Col dilaté ?	☐Yes/ ☐No
Œdèmes des Membres Inferieures		☐Yes/ ☐No			
Autres					

7. EXAMENS DE LABORATOIRE (J0) :

		Observations
Taux d'Hémoglobine:	……*g/dl*	
P.falciparum trophoz. (Thick film)*:*	……. */µl)*:	
Gametocytes (Thin film):	……. */µl)*:	
Autres		

8. TRAITEMENT(S) ADMINISTRE(S) (IPT-SP) :

Sulfadoxine-pyrimethamine(sp)	Date : ….. /…. / …... *Jr /mois /An.*	Descriptiion: ☐TPI I / ☐TPI II ☐TPI III
Autres Medicament (i)		
Autres Medicament (ii)		
Autres Medicament ii(i)		

9. FOLLOW-UP: Symptômes (J7, J14, J28, J54 and J82)

Asthénie ?	**J7**	**J14**	**J28**	**J42**	**J56**	**J70**	**J84**
Vertiges ?	…….	…….	……	…….	…….	……	…….
Nausées ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Vomissements ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Toux ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Dyspnées ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Anorexie ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Douleurs abdominales ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Diarrhée ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Eruption cutanées ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Dysurie ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Leucorrhées ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Saignements vaginaux ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Dyspareunie ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Autres symptômes ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Eruption cutanées ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Toux ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Autres symptômes 1?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Autres symptômes 2?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No

10. FOLLOW-UP: Examens Physiques (J14 to **J84)**

		J7	**J14**	**J28**	**J42**	**J56**	**J70**	**J84**
Température :		…….^{o}C)	…….^{o}C)	…….^{o}C)	…….^{o}C)	…….^{o}C)	…….^{o}C)	…….^{o}C)
Conjonctives :	Pâleurs?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Poumons :	Râles Bronchiques ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
	Râles Crépitant ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Cœur :	Souffles cardiaq.?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Abdomen (Palpations) :	Douleurs abdomens?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
	Hépatomégalie ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
	Splénomégalie ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Autres signs :	☐Yes/ ☐No	*Si oui, Citez-le(s) : ……*						

11. FOLLOW-UP: Obstetrical Examination (J14 to J84)

	J7	**J14**	**J28**	**J42**	**J56**	**J70**	**J84**
BDCF (/mins):	…….	…….	……	…….	…….	……	…….
MAF ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Contractions Utérines ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Saignement Vag. ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Leucorrhées	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Col dilaté ?	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
OMI	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No	☐Yes/ ☐No
Auttres	☐Yes/ ☐No	Si oui, citez les……					

12. FOLLOW-UP: Examens de Laboratoire et Blood spots (J14 to J84)

	J7	**J14**	**J28**	**J42**	**J56**	**J70**	**J84**
Taux d'Hémoglobine:	*……g/dl*	*……g/dl*	*……g/dl*	*……g/dl*	*……g/dl*	*……g/dl*	*……g/dl*
Test de Diagnostic Rapid :	☐Neg/☐Pos	☐Neg/☐Pos	☐Neg/☐Pos	☐Neg/☐Pos	☐Neg/☐Pos	☐Neg/☐Pos	☐Neg/☐Pos
P.falciparum trophoz. (Thick film)*:*	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:
Gametocytes (Thin film):	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:	……. */µl)*:

13. FOLLOW-UP TRAITEMENT(S) ADMINISTRE(S) (IPT-SP) :

	Day 28	Day 56	Day 84
Sulfadoxine-pyrimethamine(sp)	Date : ….. /…. / …... *Jr /mois /An.* Descriptiion: ☐TPI I / ☐TPI II ☐TPI III	Date : ….. /…. / …... *Jr /mois /An.* Descriptiion: ☐TPI I / ☐TPI II ☐TPI III	Date : ….. /…. / …... *Jr /mois /An.* Descriptiion: ☐TPI I / ☐TPI II ☐TPI III

14. Autres Traitements

		J7	**J14**	**J28**	**J42**	**J56**	**J70**	**J84**
Autre Medt 1	*Noms DCI ou autre nom*							
	Indication							
	Durées							
Autre Medt 2	*Noms DCI ou autre nom*							
	Indication							
	Durées							

15. FOLLOW-UP: Suspected Adverse Events

	Symptom or Sign or Describe	**Classification**	**Day of Onset** *(Day01-Day28)*
Adverse Event No.1	……..	☐Mild ☐Moderate ☐Severe ☐Life Threatening	…….
Adverse Event No.2	……..	☐Mild ☐Moderate ☐Severe ☐Life Threatening	…….
Adverse Event No.1	……..	☐Mild ☐Moderate ☐Severe ☐Life Threatening	…….

16. LABOUR/DELIVERY

16.1. Labour

Spontaneous			
Rupture of membranes			
Term			
Duration			
Induction			
Contractions			

16.2. Delivery

Immediate cry		
Meconium emission		
Hemorrhage		
Spontaneous placentar		
Placentar Abnormalities		

17. PHYSICAL EXAMINATION OF NEW BORN

Immediate cry			
APGAR score			
Anthropometric signs			
Vital signs			
Birth weight(classify)			
Malformation			
Others			

Appendix 2: participation consent form

Title: Efficacy and safety of intermittent preventive treatment in pregnancy

My name is Joel Mbouda, a seventh-year medical student at the FMBS yaounde. We are doing a study on the prevention of malaria in pregnancy. MiP is a dangerous disease which can be prevented with a number of strategies. The purposed of this study is to confirm that sulfadoxine-pyrimethamine (FANSIDAR) is still effective in preventing MiP.

Your participation in this study is entirely voluntary. Before you decide whether to participate, you can talk to anyone you feel comfortable with. You will receive 3 doses of 75mg and 1500mg of sulfadoxine and pyrimethamine. This medicine is recommended by the minister of health. The ministry regularly conducts studies to make sure the medicine is still working.

During the day of enrollment and follow-up, a small amount of blood will be taken from your finger. You may experience a bit of pain or fear when your finger is pricked. The pain should disappear within 1 day. The blood will be dropped on a slide or a small piece of paper. The blood will be used to see if there is malaria in your blood. Nothing else will be done with your blood.

The study will take place over 84 days. During that time, you will have to come to the health facility for 1 hour on day 28, 56 and 84 of the 84 days. At each visit you will be examined.

We will not share the identity of participants in the study with anyone. The information we collect from this study will be kept confidential. Any information collected about you will have a number on it instead of your name. Only the study team members will know what your number is, and we will lock that information up.

Certificate of consent

I have been invited to participate in a study of a medicine use to prevent malaria in pregnancy. I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any question that I asked has been answered to my satisfaction. I consent voluntarily to participate in this study.

Print name of participant ……

Signature of participant ……..

Date……..

Appendix 3: Application for ethical clearance

JOEL MBOUDA ISAMBI

7th Year General Medicine

Address: jabiajoel1@gmail.com

Tel: +237 675511439

The President,

Institutional Ethics and Research

Committee,

Faculty of Medicine and Biomedical

Sciences, University of Yaoundé 1.

Sir,

AN APPLICATION FOR ETHICAL CLEARANCE

I am most honored to write you in view of obtaining an ethical clearance.

I am a 7th year general medicine student in the faculty of medicine and biomedical sciences, University of Yaoundé 1 and for MD thesis I intend working on parasitological and Obstetrical outcome of intermittent preventive treatment in pregnant women using sulfadoxine-pyrimethamine, under the supervision of professor Wilfred Fon Meacham. We believe that our study will identify any failures in the preventive effects of sulfadoxine-pyrimrthamine that might herald the emergence of a resistance phenotype in our country.

For this study, ethical considerations shall be of utmost importance and obtaining an ethical clearance is indispensable.

While waiting for a favorable response, accept sir, my best regards.

Attached

-copy of research protocol

-copy of receipt of school

SUPERVISOR

Sincerely,

JOEL MBOUDA ISAMBI

JOEL MBOUDA ISAMBI

7th Year General Medicine

Address: jabaijoel1@gmail.com

Tel: +237 675511439

The DIRECTOR.

Medical center Mgr Jean Zoa

Yaounde.

Sir,

AN APPLICATION FOR AUTORIZATION TO CONDUCT A RESEARCH STUDY IN YOUR HEALTH STRUCTURE FOR AN MD DEGREE OBTENTION

I am most honored to write you in view of obtaining an ethical clearance.

I am a 7th year general medicine student in the faculty of medicine and biomedical sciences, University of Yaoundé 1 and for MD thesis, I intend working on the Parasitological and Obstetrical outcomes of intermittent preventive treatment in pregnant women using sulfadoxine-pyrimethamine. This under the supervision of professor Wilfred Fon Meacham. We believe that our study that our study will identify any failure in the preventive effects of sulfadoxine-pyrimrthamine that might herald the emergence of a resistance phenotype in our country.

For this study, authorizations from the hospital authorities shall be of utmost importance and obtaining an ethical clearance is indispensable.

While waiting for a favorable response, accept sir, my best regards.

Attached

-copy of research protocol

-copy of receipt of school

SUPERVISOR

Sincerely,

JOEL MBOUDA ISAMBI

UNIVERSITÉ DE YAOUNDÉ I
FACULTÉ DE MÉDECINE ET DES SCIENCES BIOMÉDICALES
COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE
Tel/ fax : 22 31-05-86 22 311224
Email: decanatfmsb@hotmail.com

THE UNIVERSITY OF YAOUNDE I
FACULTY OF MEDICINE AND BIOMEDICAL SCIENCES
INSTITUTIONAL ETHICAL REVIEW BOARD

Ref. : N° 0847 /UY1/FMSB/VDRC/DAASR/CSD

CLAIRANCE ÉTHIQUE

10 JUIN 2024

Le COMITÉ INSTITUTIONNEL D'ÉTHIQUE DE LA RECHERCHE (CIER) de la FMSB a examiné

La demande de la clairance éthique soumise par :

M.Mme : JOËL MBOUDA ISAMBI **Matricule: 16M101**

Travaillant sous la direction de :
- **Pr MBACHAM Wilfred**
- **Pr ESSIBEN Felix**
- **Dr Valentine NCHAFOR NDIKUM**

Concernant le projet de recherche intitulé : **Parasitological efficacy and obstetrical outcome of Sulfadoxine-Pyremethamine in the intermittent preventive treatment of malaria in pregnancy**

Les principales observations sont les suivantes

Evaluation scientifique	
Evaluation de la convenance institutionnelle/valeur sociale	
Equilibre des risques et des bénéfices	
Respect du consentement libre et éclairé	
Respect de la vie privée et des renseignements personnels (confidentialité) :	
Respect de la justice dans le choix des sujets	
Respect des personnes vulnérables :	
Réduction des inconvénients/optimalisation des avantages	
Gestion des compensations financières des sujets	
Gestion des conflits d'intérêt impliquant le chercheur	

Pour toutes ces raisons, le **CIER** émet un avis **favorable** sous réserve des modifications recommandées dans la grille d'évaluation scientifique.

L'équipe de recherche est responsable du respect du protocole approuvé et ne devra pas y apporter d'amendement sans avis favorable du **CIER**. Elle devra collaborer avec le **CIER** lorsque nécessaire, pour le suivi de la mise en œuvre dudit protocole.
La clairance éthique peut être retirée en cas de non - respect de la réglementation ou des recommandations sus évoquées.
En foi de quoi la présente clairance éthique est délivrée pour servir et valoir ce que de droit

LE PRESIDENT DU COMITE ETHIQUE