

Gestational malaria in Kisangani : Efficacy of Mefloquine vs Sulfadoxine-Pyrimethamine in Intermittent Preventive Treatment : A Study Protocol for a randomized controlled clinical trial

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Study protocol

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Abstract

Background : In order to reduce malaria-related morbidity and mortality during pregnancy, WHO recommends : Insecticide-treated mosquito nets, Intermittent Preventive Treatment of malaria in pregnancy, Prompt and effective case management. Nevertheless, several cases of resistance to Sulfadoxine-Pyrimethamine, used in intermittent preventive treatment, and to Chloroquine are reported in sub-Saharan Africa and in the Democratic Republic of the Congo. The prevalence of malaria among pregnant women remains high in Africa in general, and in the Democratic Republic of Congo in particular. This issue leads us to conduct this study, which aims at proposing an alternative to SP for preventing malaria in pregnant women. **Materials and methods :** From June 1 to October 31, 2019, we enrolled pregnant women from five health facilities in Kisangani for randomized, single-blind controlled clinical trials to compare the efficacy of two intermittent preventive treatment regimens in Kisangani pregnant women, selected before 18 th weeks of amenorrhea. The first regimen consists of 4 doses of Sulfadoxine-Pyrimethamine starting at the selection time and spaced at least 4 weeks during pregnancy. Each dose is made of 3 tablets of 525 mg Sulfadoxine-Pyrimethamine. The second regimen consists of 2 doses of Mefloquine during pregnancy. The first dose is taken at the selection time and the second dose between the 28 th and 32 nd weeks of amenorrhea. Each dose is made of 3 tablets of 250 mg Mefloquine. The efficacy criteria for these two regimens are placental malaria parasitemia, low birth weight of newborn and maternal anemia at delivery. The safety criterion was the occurrence of major side effects. **Discussion :** There are not enough randomized clinical trials assessing the efficacy of Mefloquine for the intermittent preventive treatment of malaria in African pregnant women, hence the recommendation for clinical trials. The present study is the only one that conducts such assessment in a hyper-endemic area with resistance to Sulfadoxine-Pyrimethamine and Chloroquine. The findings are therefore intended to promote the use of Mefloquine as the best alternative to Sulfadoxine-Pyrimethamine in the intermittent preventive treatment of malaria. **Clinical trial registration :** PACTR201905899965726. **Key words :** Intermittent preventive treatment, efficacy, safety, Mefloquine, Sulfadoxine-Pyrimethamine, Kisangani.

Background

Known since ancient times, malaria remains a public health problem. The population likely to be infected with the parasite and develop the disease is 3.2 billion, and the risk is high (more than 1 in 1,000 chance of contracting malaria during one year) for 1.2 billion people[1]. According to 2013 estimates, 198 million cases of malaria (124-283 million) and 584,000 associated deaths (ranging 367,000 - 755,000) have been identified worldwide, the number of malaria cases is estimated at 214 million in 2015 (149-303 million) with 438,000 deaths (236,000 - 635,000)[1, 2].

According to the WHO, the disease is particularly prevalent in Africa, where 90% of deaths from malaria in the world are recorded[1]. In 2015, most cases of malaria (88%) and related deaths (90%) were recorded in the African region [2]. Children under 5 years and pregnant women are the main victims [3, 4].

The Democratic Republic of Congo (DRC) is the second sub-Saharan African country most affected by malaria after Nigeria. These two countries alone, along with India, account for 40% of malaria cases [5]. In Kisangani, in northeastern DRC, a study conducted in six health facilities, from January 1 to September 30, 2017, revealed a 27.56% prevalence of gestational malaria.[6].

In order to help reduce malaria-related morbidity and mortality, WHO recommends a three-pronged approach to malaria in pregnancy which includes:

- Insecticide-treated mosquito nets (ITNs),
- Intermittent preventive treatment in pregnancy (IPTp),
- Prompt and effective case management.

Strengthening control and prevention measures has proved to dramatically reduce malaria burden in some places. Thus, WHO recommends IPTp using SP (IPTp-SP) and ITNs to reduce maternal anemia and low birth weight by 40% [3, 7].

Sulfadoxine-Pyrimethamine (SP) has long been proven to be the chosen medicine for malaria prophylaxis for its efficacy, along with its long half-life justifying a single dose and thus adherence to treatment and few side effects[8, 9]. Several authors among them Losimba et al. [10], and Brabin et al. [11], Tinto et al. [12] reported that this combination was effective.

However, for some time, the development of SP resistance in the world and in sub-Saharan Africa has been noted. Basuki S. et al. [13] identified cases of SP resistance in Indonesia. Several cases of SP resistance have been reported in Africa [14-20]. Nosten and Mc Gready [21] considered in 2015 that SP is a failure in various parts of Africa and that evidence for the beneficial effects of IPTp-SP was low. Ruh et al. [22] also made these findings in the DRC. In DRC, in the city of Kisangani, Labama et al. [6] found that SP does not reduce the gestational malaria risk. This situation raises serious concerns regarding the use of this combination for IPTp[23]. Garner and Brabin [24], after a review of randomized controlled trials of IPT in malaria-endemic areas concluded that additional studies are required to establish whether IPT has benefits on prompt and effective management of clinical malaria. Thus, several alternative options to SP are currently being evaluated and proposed, SP plus Azithromycin or Artesunate, Chloroquine, SP plus Chloroquine, Mefloquine (MQ), SP plus Piperaquine, etc.[25-28]. The difficulty of administering some of these regimens is that resistance has developed for chloroquine, Piperaquine has been used like mass prophylaxis and curative treatment in China since 1978, Artesunate is used for curative treatment in combination with Amodiaquine in the DRC and Azithromycin happens to be costly [16, 25]. Clerk et al. [20] reported that the effect of IPT with Artesunate-Amodiaquine or SP-Artesunate-Amodiaquine on maternal anemia and low birth weight newborns were comparable to the effects of IPTp-SP.

According to a study by Gosling et al. comparing the efficacy of SP, Chlorproguanil-Dapsone and MQ, it was noted that MQ had a more superior protective effect than the others. According to the Belgian Pharmaceutical Information Center [31], MQ is recommended for prophylaxis in areas with chloroquine resistance. Chloroquine resistance continues to persist in most countries affected by malaria[32], and the

DRC is not spared. Indeed, after removing chloroquine from the DRC's malaria treatment policy 11 years ago, still, Juliao et al. [32] and Mvumbi et al. [33] have identified markers of chloroquine resistance.

In view of the above, we thought it was appropriate to compare MQ with SP for IPTp in Kisangani, an endemic malaria area with SP and Chloroquine high-level resistance.

In order to conduct this study, we considered the following research question:

Will the prevalence of placental malaria, maternal anemia at delivery and low birth weight of newborns in Kisangani pregnant women who received MQ as IPTp be lower than in those who received SP.

Hypothesis

Since MQ has a long half-life, with a low rate of resistance in sub-Saharan Africa [26], the following result can be expected : MQ is more effective than SP in IPTp in Kisangani.

Material And Methods

Objectives

This study aims to :

1. To compare the efficacy of MQ versus SP in IPTp in Kisangani ;
2. To compare the safety of MQ versus SP in Kisangani pregnant women.

Type, framework and period of study

The study is a single blind, randomized controlled clinical trial that compares two regimens of IPTp – trial in which only the investigators know what treatment or medication the participants receive, and the participants do not know.

The study has been conducted in Kisangani since June 1, 2019 and will continue until all study participants give birth. One health facility per health area (HA) was selected for 4 of 5 HA that the city of Kisangani has, except in the HA of Kabondo where 2 health facilities were selected. The choice of these five health facilities was motivated by the fact that these facilities are very popular with pregnant women, and they have qualified medical biotechnologists trained in the technique of blood smear (BS) and parasite density. Thus, Kabondo (Kabondo's HA) and Makiso-Kisangani's (Makiso / Kisangani's HA) referral general hospitals (RGH) were selected ; the reference health centers Foyer (RHC) (Kabondo HA), Saint Joseph (Tshopo HA) and Matete (Mangobo HA) were selected, as well. The rationale for selecting these two health facilities in the Kabondo's HA was that the Makiso-Kisangani's RGH being eccentric, for reasons of proximity, a part of its target population, especially pregnant women living in the municipality of Kisangani, generally attend the Kabondo's RGH. No health facilities in Lubunga's HA was selected because this HA is located on the other bank of the Congo River, in the municipality which bears the same

name ; This geographical situation would not allow prompt and effective management of potential major side effects.

Study population

The study population is composed of pregnant women who live in Kisangani and the surrounding area for more than 2 weeks prior the selection and who attend antenatal care (ANC) in the selected health facilities during the period of June 1 to November 30, 2019.

Sample size

To calculate the sample size, we referred to González *et al.* [34] who found a prevalence of placental parasitaemia of 3.2% in pregnant women under MQ and 4.6% in those under SP.

Thus, we are going to recruit at least 148 pregnant women, of whom 74 with IPTp-SP and 74 with IPTp using MQ (IPTp-MQ).

Inclusion criteria

Are included in the study pregnant women who:

- begin their ANC in the selected health facilities, with gestational age under 18 weeks of amenorrhea ;
- have not received IPTp yet ;
- give their informed consent.

Exclusion criteria

Are excluded pregnant women with :

- positive HIV serology ;
- history of known sickle cell disease ;
- history of neurological (e.g. epilepsy), psychiatric, renal or hepatic affections ;
- history of allergy to sulfonamides or MQ ;
- received an antimalarial or other medicine within 15 days of selection ;
- have consumed medicinal herbal tea within 15 days prior to the selection.

Criteria for withdrawal from the study

Participants with at least one of the following criteria will be subsequently excluded:

1. withdrawal of consent ;
2. study medication's major side effect ;
3. failure to comply with the TPIp regimen ;
4. delivery out of the follow-up health facility.

All withdrawal details are recorded in the data collection sheet and the register of discarded cases. Upon withdrawal, the ANCs will continue normally. Any details related to withdrawal or loss of follow-up will be recorded in the side effects sheets and notified to the study follow-up committee.

Recruitment and randomization of participants

Respondents are selected during the ANCs, since June 1st and ongoing till October 31st, 2019.

When registering pregnant women, the investigators obtain their informed consent.

Medical biotechnologists perform HIV screening (Determine HIV Rapid Test) of eligible pregnant women, after obtaining their approval. Positive cases are excluded and referred to the provincial laboratory of the National HIV / AIDS Control Program (NHCP) in Kisangani for confirmation of diagnosis and possible management.

During selection, each participant is given a unique code. This code comprises the initial of the health facility where the participant is selected, followed by a serial number. Each participant's code is recorded in a case register. Then the participants are randomized. Thus, the first selected receives SP while the second receives MQ.

Intervention

Study medication

As study medication, we use the MQ of INCAS PHARMACEUTICAL marketed under the brand name of Meflotas ®, presented in the blister of two tablets of 250 mg each. B. No: NY0399. MFD.: Feb. 2019. Exp.: Apr. 2021.

As a control medication, we use the SP of GUILIN PHARMACEUTICAL marketed under the brand name of G-COSPE®, presented in a box of 1000 tablets each dosed with 500 mg of Sulfadoxine and 25 mg of Pyrimethamine. B. No.: 75892. Mfr.: 03/18. Exp.: 03/23.

Before starting the trial, all the study medications were controlled by the quality assurance laboratory of the Office Congolaise de Contrôle in Kisangani.

Supply and control of medicines

The DRC's National Malaria Control Program (PNLP) provides the public maternity wards with free SP for pregnant women during ANCs.

The MQ was imported from India, in strict compliance with the guidelines of good medicine distribution practices applicable in DRC [35]. Medicines go through all control chains. In Kisangani, the medicines underwent quality analysis and certification by the control laboratory of the Office Congolaise de Contrôle.

Storage and distribution of medicines

After a new labeling, the medicines are stored in the pharmacy of Kisangani University Clinics, according to the storage standards.

At each ANC session, the study supervisor provides the health facilities with the quantity of medicines proportional to the number of the daily beneficiaries. The health facilities record the quantity in the stock records for medicines.

Treatment delivery

Before starting the trial, in addition to the authorization of the Ethics Committee of Kisangani University, the authorizations were obtained from the Provincial Chief Medical Officer of Tshopo.

Participants are put under either of the IPT regimens that we compare. The first regimen consists of 4 doses of SP starting at the selection time and spaced at least 4 weeks during pregnancy. Each dose is made of 3 tablets of 500 mg Sulfadoxine and 25 mg Pyrimethamine taken during ANC under nurse supervision.

The second regimen consists of 2 doses of MQ during pregnancy. The first dose is taken at the selection time and the second dose between the 28th and 32nd weeks of amenorrhea. Each dose is made of 3 tablets of MQ - 1 tablet (250 mg) every 8 hours at home and during the meal. Every time participants have to take their dose of Mefloquine, during ANC, the investigators give them the 3 tablets and explain the dosage and methods.

The administered regimen and the date of administration are recorded in the data collection sheet and in the case register ; the code of each study participant is recorded along with the IPTp regimen.

Concomitant preventive measures

Participants regularly receive ANC. During the selection, they are given iron-folate and each is given a new ITNs.

Additional recommendations

Participants are also sensitized on the environment sanitation. Antimalarial self-medication is discouraged, pregnant women are encouraged to return to hospital whenever they have symptoms of malaria. Herbal tea made from medicinal plants is not recommended.

Management of side effects

Participants are followed at the hospital on day 1, day 2, day 7 and day 14 after taking medication, for registration and management of any side effects. In order to record any event (along with the nature and timing of the event) that occurred after taking study medications, investigators use questionnaires. Investigators also make sure the participants that use MQ comply with the regimen dosage and methods of taking.

All the symptoms reported by the participants taking the study medication are recorded in the register of monitoring side effects. The study doctor, who is not a member of the investigative team, assesses these symptoms, perform a physical examination and, if necessary, para clinical examinations. Only reported events related to the 2 study medications are considered as side effects. The other complaints are recorded in a sheet and analyzed by the pharmacovigilance center in order to determine whether or not those events are related to taking medications.

Participants with minor side effects are followed in the health facilities where the trials are conducted, providing them with outpatient care, as the study doctor recommended. Participants with major side effects requiring hospitalization are excluded from the study and are followed in these health facilities where trials are conducted, or referred to Kisangani university clinics. For pregnancy continued care, participants are put under another IPTp regimen. Major side effects of MQ include : suicidal tendencies, anxiety, hallucinations, depression, unusual thinking and behavior, extreme fear, agitation, nightmares, uncontrollable vomiting, debilitating headache, coca-cola urine, jaundice and dyspnea. Redness of the skin, itching, rash (e.g. hives) are considered major side effects of SP.

The University's Ethics Committee will conduct a mid-term assessment of side-effect data and decide if trials can continue.

Participants will be followed until delivery, they will receive usual antenatal care, and information on clinical malaria, use of antimalarials, and potential side effects of study medications will be given to them. Participants who will develop clinical malaria during pregnancy will be treated according to the malaria treatment policy recommended in the DRC.

Schedule of enrolment, interventions, and assessments

To write the study protocol, we completed the SPIRIT checklist and we constructed a SPIRIT figure.

Data collection

Data collection is prospective.

Before starting the data collection, the investigators (midwives or nurses and medical biotechnologists) were briefed on the research protocol and study medications. Midwives or nurses (2 per health facility) were then trained on the randomization and interviewing technique, details of 2 IPTp regimens studied,

surveillance of the respondents, identification and record of side effects. The study doctor (1) was trained on the identification and management of side effects.

Upon enrollment of participants, trained nurses or midwives obtain informed consent. Using a standardized questionnaire, they collect information on the socio-professional characteristics and history of the respondents, in particular the date of the last menstrual period, the parity, the gesture, the age of the last child. Questions are written in French, but if necessary, the respondents are interviewed in Lingala or Swahili. After a complete physical examination, the laboratory technicians perform the mandatory para clinical examinations for pregnancy monitoring, including hemoglobin and BS test. The trained nurses or midwives also randomize the respondents and administer the study medications. The information collected during the interview, the results of the physical and laboratory examination and the IPTp regimen are recorded in the data collection sheet.

After taking medication, respondents return to the hospital on day 1, day 2, day 3 and day 7. In hospital, participants are interviewed about the occurrence of side effects. Respondents with side effects also return to the hospital on day 14. All reported side effects are recorded in the data collection sheet and the register of side effects. Compliance with the dosage and methods of taking is also checked for participants who used Mefloquine.

During pregnancy, the respondents regularly follow the ANC's and all the events occurred are recorded in the data collection sheet.

At the time of delivery, upon admission of participants to the delivery room, nurses or midwives fully examine them and medical biotechnologists perform hemoglobin test. Then, maternal anemia at delivery will be considered to have a hemoglobin level of less than 11gr / dl. The results of examinations will be recorded in the data collection sheet or in the laboratory register.

Immediately after delivery, nurses or midwives will thoroughly examine newborns while weighing them using the SH-8008 electronic baby scale. The weight details will be confirmed after double-checking (re-weigh) before being recorded in the data collection sheet and in the delivery register. A weight lower than 2500 gr at birth will be considered as low birth weight. The medical biotechnologists of the study will proceed to the preparation of the placental stamp BS. The slides will be read at the Provincial Public Health Laboratory (PPHL) in Kisangani and the results will be recorded in the laboratory register.

To ensure the reliability, the data collected by one investigator will first be counter-checked by another and then by the study supervisor. And for the quality control of the laboratory results, 10% of the randomly positive selected and 10% of the randomly negative selected PPHL samples will be transferred to the Institut National de Recherches Biomédicales in Kinshasa for the same analysis. The concordance rate of the BS results will be determined by calculating the Kappa number.

The data collected will be encoded by an independent data manager.

Blood sample

-Training

Medical biotechnologists were briefed on hemoglobin assay techniques using the Hemocue Hb Hemoglobinometer according to the manufacturer's instructions, taking placental stamps, spreading blood smear on the slide and transporting slides according to the guidelines of the National Malaria Control Program (NMCP). They were also briefed on Determine HIV rapid test.

- Collecting blood from placental stamps

Immediately after delivery, medical biotechnologists will clean the placenta ; they will superficially cut its maternal surface and will apply a blade on the incised placental surface.

Laboratory investigations

- Placental parasitaemia

The study supervisor (1) will transport, according to the standards, the smear spread on slides to the Provincial Public Health Laboratory. The medical biotechnologists will stain the smear for 10 minutes to 10% diluted giemsa solution. After preparation, they will read the microscope 100X objective. The diagnosis of malaria will be considered when trophozoites or other plasmodium development stages are present in the sample.

Efficacy criteria

Efficacy criteria will be primarily placental parasitaemia and secondly the low birth weight of the newborn (weight < 2500 g) and maternal anemia at delivery (hemoglobin <11g / dl).

The safety criterion is the occurrence or not of major side effects.

Data analysis

Only data of participants who will give birth in their follow-up health facilities with good compliance with IPTp regimen will be analyzed.

The collected data will be first encoded and then analyzed using the software EPI Info version 7.2.2.6 and Xlstat 2019.

To describe the sample, the frequency and percentage, the means and their standard deviations, the median and areas of variation will be calculated;

To compare the proportions, Pearson's chi squared Fisher's or exact test at the significance level of < 0.05.

To compare the mean birth weights and mean mothers' hemoglobin levels, the ANOVA will be used. The difference will be significant if the *P*-value is < 0.05 at the 95% threshold.

To measure the strength of the association, the relative risk and its 95% confidence interval will be determined.

To eliminate the confounding factors, a multivariate analysis with conditional logistic regression will be performed.

Discussion

In conducting a clinical trial, we intend to prove that MQ is the best alternative to replace SP in IPTp in Kisangani, DRC. IPTp-MQ would reduce placental parasitaemia malaria, low birth weight of newborns, and maternal anemia at delivery. Some studies in other countries have shown that the efficacy of MQ is superior to that of SP in IPTp [26, 29, 36, 37]. However, it has been reported that SP is better tolerated than MQ. In his literature review, Raquel et al. found that there were not enough randomized clinical trials assessing the efficacy and safety of MQ for IPTp in Africa and recommended further trials[34].

Our clinical trial is the only one that compares the efficacy and safety of MQ to those of SP in IPTp in a hyper-endemic area with SP and Chloroquine resistance.

The findings of the present clinical trial, which we will share with the NMCP of the DRC, are therefore supposed to promote the choice of MQ as the best alternative to SP in IPTp of malaria among pregnant women.

Status Of The Trials

This protocol was registered on the Pan African Clinical Trial Registry (www.pactr.org) on May 13, 2019. The identification number for the registry is PACTR201905899965726.

The clinical trials are in progress. Recruitment began on June 1, 2019. It will be approximately completed on November 15, 2019.

List Of Abbreviations

ANC : Antenatal Care

BS : blood smear

DRC : Democratic Republic of Congo

HA : health area

IPTp : Intermittent Preventative Treatment of malaria in pregnancy

IPTp-MQ : IPTp using MQ

IPTp-SP : IPTp using SP

ITNs : Insecticide-treated mosquito net

MQ: Mefloquine

NHCP : National HIV/AIDS Control Program

NMCP : National Malaria Control Program

PPHL : Provincial Public Health Laboratory

RGH : referral general hospitals

RHC : reference health centers Foyer

SP: Sulfadoxine-Pyrimethamine

Declarations

Ethical considerations

Ethical approval for the study was obtained from the Ethics Committee of Kisangani University (Approval No. UNIKIS / CER / 006/2018).

Additional authorizations were obtained from the Provincial Chief Medical Officer of Tshopo.

Before participating in the study, pregnant women give an informed consent. Data collected are confidential.

Consent for publication

Not Applicable.

Data and material availability

The data used and / or analyzed in this study will be available from the corresponding author upon reasonable request.

Conflicts of interest

The authors state that there are no conflicts of interest.

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study as well as the writing of our manuscript.

Contributions of the authors

Doctors Labama and Bosenge, and Professor Losimba designed the protocol. Doctors Labama, Bosenge and Maindo wrote the manuscript. Professors Manga, Ahuka, Marini, Katenga and Losimba have revised the protocol. Professors Marini and Manga validated the protocol. All authors read and enriched the manuscript.

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References

1. World Health Organization. World Malaria Report 2011. WHO, Genève; 2014.
2. World Health Organization. World Malaria Report 2015. WHO, Genève ; 2016.
3. World Health Organization. World Malaria Report 2011. WHO, Genève; 2011.
4. World Health Organization. World Malaria Report 2008. WHO, Genève ; 2008.
5. World Health Organization. World Malaria Report 2008. WHO, Genève ; 2012
6. Labama O.N., Bosenge N.J-D., Maindo A.M-A., Modia O.A., Katenga B.G., Likwela L.J.. et *al*. Prevalence of Gestational Malaria in Kisangani, Democratic Republic of Congo. Open Journal of Obstetrics and Gynecology, 2018, 8, 854-866 disp. <http://www.scirp.org/journal/ojog>
7. World Health Organization. World Malaria Report 2005. WHO, Genève; 2005.

8. Maiga O.M., Kayentao K., Traore´ B.T., Djimde A., Traore´ B., Traore´ M. et al. Superiority of 3 Over 2 Doses of Intermittent Preventive Treatment With SulfadoxinePyrimethamine for the Prevention of Malaria During Pregnancy in Mali: A Randomized Controlled Trial. *Clinical Infectious Diseases* 2011;53(3):215–223
9. Gies S., Oumar C.S, Tiemegna O.F. et D’Alessandro U. Individual efficacy of intermittent preventive treatment with sulfadoxine–pyrimethamine in primi- and secundigravidae in rural Burkina Faso: impact on parasitaemia, anaemia and birth weight. *Tropical Medicine and International Health*. volume 14 no 2 pp 174–182 february 2009. doi:10.1111/j.1365-3156.2008.02215.x
10. Losimba L.J, d’Alessandro U., Labama L. B., E. Mugisha S.E., Gasana G., Kakoma J. B. et al. Effet du traitement préventif intermittent (TPI) de la femme enceinte à la sulfadoxine-pyriméthamine (SP) sur le poids de naissance des enfants dans un milieu à résistance élevée du Plasmodium falciparum à la SP à l’Est de la République Démocratique du Congo (RDC). *Rwanda Medical Journal*. Dec. 2010, Vol. 68 (4)
11. Brabin L., Stokes E., Dumbaya I. et Owens S. Rural Gambian women's reliance on health workers to deliver sulphadoxine – pyrimethamine as recommended intermittent preventive treatment for malaria in pregnancy. *Malaria Journal* 2009, 8:25
12. Tinto H., Ouédraogo J.B., Zongo I., Van O.C., Van M.E., Tinga R.G. et al. Sulfadoxine–Pyrimethamine efficacy and selection of *plasmodium falciparum dhfr* mutations in burkina faso before its introduction as intermittent preventive treatment for pregnant women. *J. Trop. Med. Hyg.*, 76(4), 2007, pp. 608–613
13. Basuki S., Fitriah, Risamasu M.P, Kasmijati, Ariami P., Riyanto S. et al. Origins and spread of novel genetic variants of sulfadoxine–pyrimethamine resistance in Plasmodium falciparum isolates in Indonesia. *Malaria Journal* (2018) 17:475. <https://doi.org/10.1186/s12936-018-2597-6>
14. Ruizendaal E., Tahita C.M., Geskus B.R., Versteeg I., Scott S., d’Alessandro U. et al. Increase in the prevalence of mutations associated with sulfadoxine–pyrimethamine resistance in Plasmodium falciparum isolates collected from early to late pregnancy in Nanoro, Burkina Faso. *Malaria Journal* (2017) 16:179. DOI 10.1186/s12936-017-1831-y
15. Cisse M., Awandare G.A., Soulama A., Tinto H., Hayette M-P et Guiguemdé R.T. Recent uptake of intermittent preventive treatment during pregnancy with sulfadoxine–pyrimethamine is associated with increased prevalence of Pfdhfr mutations in Bobo-Dioulasso, Burkina Faso. *Malaria Journal* (2017) 16:38
16. Ngondi M.J., Ishengoma S.D., Doctor M.S., Thwai L.K., Keeler C., Mkude S. et al. Surveillance for Sulfadoxine-Pyrimethamine resistant malaria parasites in the Lake and Southern Zones, Tanzania, using pooling and next-generation Sequencing. *Malaria Journal* (2017) 16:236. DOI 10.1186/s12936-017-1886-9
17. Bertin G., Briand V., Bonaventure D., Carrieu A., Massougbodji A., Cot M. et al. Molecular markers of resistance to sulphadoxinepyrimethamine during intermittent preventive treatment of pregnant women in Benin. *Malaria Journal* 2011, 10:196. <http://www.malariajournal.com/content/10/1/196>

18. Jiang T., Chen J., Fu H., Wu K., Yao Y., Urbano M.E.J. et al. High prevalence of Pfdhfr–Pfdhps quadruple mutations associated with sulfadoxine–pyrimethamine resistance in *Plasmodium falciparum* isolates from Bioko Island, Equatorial Guinea. *Malaria Journal* (2019) 18:101. <https://doi.org/10.1186/s12936-019-2734-x>
19. Ravenhall M., Diez B.E., Mipando M., Jensen T.R.A., Sutherland J.C., Roper C. et al. Characterizing the impact of sustained sulfadoxine/pyrimethamine use upon the *Plasmodium falciparum* population in Malawi. *Malaria Journal* (2016) 15:575. DOI 10.1186/s12936-016-1634-6
20. Braun V., Rempis E., Schnack A., Decker S., Rubaihayo J., Mbona T.N. et al. Lack of effect of intermittent preventive treatment for malaria in pregnancy and intense drug resistance in western Uganda. *Malaria Journal* (2015) 14:372. DOI 10.1186/s12936-015-0909-7
21. Nosten F. et McGready R. Intermittent presumptive treatment in pregnancy with sulfadoxine–pyrimethamine: a counter perspective. *Malaria Journal* (2015) 14:248. DOI 10.1186/s12936-015-0765-5
22. Ruh E., Bateko J.P., Imir T. et Taylan-Ozkan A. Molecular identification of sulfadoxine-pyrimethamine resistance in malaria infected women who received intermittent preventive treatment in the Democratic Republic of Congo. *Malaria Journal* (2018) 17:17. <https://doi.org/10.1186/s12936-017-2160-x>
23. Gosling R.D., Cairns M.E., Chico R.M. et Chandramohan D. Intermittent preventive treatment against malaria: an update. *Expert Rev. Anti Infect. Ther.* 8(5), (2010). DOI: 10.1586/eri.10.36
24. Garner P. et Brabin B. A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas. *Bulletin of the World Health Organization*, 1994, 72 (1): 89-99. World Health Organization 1994
25. Yorokpa D.J., Matangila J., Lutumba P. et Van geertruyden J-P. Intermittent preventive treatment: efficacy and safety of sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine plus piperazine regimens in schoolchildren of the Democratic Republic of Congo: a study protocol for a randomized controlled trial, *Trials* 2013, 14:311. <http://www.trialsjournal.com/content/14/1/311>
26. Briand V., Bottero J., Noel H., Masse V., Cordel H., Guerra J. et al. Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine. *J Infect Dis* 2009, 200:991–1001.
27. Issaka S., Oduro R. A., Mulenga M., Dieng Y., Ogutu B., Tiono B.A. et al. Efficacy and safety of a combination of Azithromycine and chloroquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in two multi-country randomised clinical trials in African adults. *Sagara et al. Malaria Journal* 2014, 13 :458. <http://www.malariajournal.com/content/13/1/458>
28. Kalilani L., Mofolo I., Chaponda M., Rogerson J.S., Alker P.A., Kwiek J.J. et al. A Randomized Controlled Pilot Trial of Azithromycin or Artesunate Added to Sulfadoxine-Pyrimethamine as Treatment for Malaria in pregnant women. *PLoS ONE*. November 2007, Issue 11.
29. Gosling R.D., Gesase S., Mosha J.F., Carneiro I., Hashim R., Lemnge M. et al. Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a

- randomised, double-blind, placebo-controlled trial. *Lancet* 2009, 374:1521–1532.
30. Centre belge d'Information Pharmacothérapeutique. Répertoire commenté des médicaments 2019. 32ème édition. Disp. www.cbip.be ou bcfi.be consulté le 25 août 2019 vers 13h02
 31. Ocan M., Akena D., Nsoya S., Kanya R.M., Senono R., Kinengyere A.A. et al. Persistence of chloroquine resistance alleles in malaria endemic countries: a systematic review of burden and risk factors. *Malaria Journal* (2019) 18:76. <https://doi.org/10.1186/s12936-019-2716-z>
 32. Juliao C.P., Sosa S., Gonzalez D.L., Padilla N., Ortiz L., Goldman I. et al. Importation of chloroquine-resistant *Plasmodium falciparum* by Guatemalan peacekeepers returning from the Democratic Republic of the Congo. *Malaria Journal* 2013, 12:344. <http://www.malariajournal.com/content/12/1/344>
 33. Mvumbi M.D., Boreux R., Sacheli R., Lelo M., Lengu B., Situakibanza N-T. et al. Assessment of pfcr1 72-76 haplotypes eight years after chloroquine withdrawal in Kinshasa, Democratic Republic of Congo. *Malaria Journal* 2013, 12:459. <http://www.malariajournal.com/content/12/1/459>
 34. Raquel G, Urban H, Brian G et Clara M. Mefloquine safety and tolerability in pregnancy: a systematic literature review. *Malaria Journal* 2014, 13:75. <http://www.malariajournal.com/content/13/1/75>
 35. Direction de la pharmacie et du Médicament. Lignes Directrices des Bonnes Pratiques de Distribution (BPD) applicables en RDC. Ministère de la Santé Publique, RDC, Septembre 2015
 36. Briand V., Cottrell G., Massougboji A. et Cot M. Intermittent preventive treatment for the prevention of malaria during pregnancy in high transmission areas. *Malaria Journal* 2007, 6:160. doi:10.1186/1475-2875-6-160
 37. Briand V., Escolano S., Journot V., Massougboji A., Cot M. et Tubert-Bitter P. Mefloquine versus Sulfadoxine–Pyrimethamine for Intermittent Preventive Treatment in Pregnancy : A Joint Analysis on Efficacy and Tolerability. *Am. J. Trop. Med. Hyg.*, 93(2), 2015, pp. 300–304

Figures

TIMEPOINT**	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
	-t ₁	0	t ₁	t ₂	t ₃	t ₄	etc.	t _x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
<i>[List other procedures]</i>	X							
Allocation	X	X						
INTERVENTIONS:								
<i>[Intervention A]</i>			X		X			
<i>[Intervention B]</i>			X	X	X	X		
<i>[List other study groups]</i>			←————→					
ASSESSMENTS:								
<i>[List baseline variables]</i>	X	X	X	X	X	X		
<i>[List outcome variables]</i>			X	X	X	X	etc.	X
<i>[List other data variables]</i>		X	X	X	X	X	etc.	X

Figure 1

Schedule of enrolment, interventions, and assessments

Supplementary Files

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