ISRCTN45944555 https://doi.org/10.1186/ISRCTN45944555

Assessing the benefits of using effective malaria diagnostic tests in preventing complications associated with malaria in pregnancy in a high-risk malaria area of Nchelenge in Zambia

Submission date
02/04/2024

Recruitment status
No longer recruiting

Registration date
11/04/2024

Overall study status
Completed

Last Edited
24/03/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims

Pregnant women are one of the groups most susceptible to malaria in Africa, with a higher risk of severe disease, fetal loss, and adverse birth outcomes including premature and low-birth-weight (LBW) infants. Intermittent presumptive treatment in pregnancy with sulfadoxine-pyrimethamine (IPTp-SP) is a life-saving intervention for both mothers and their offspring but increasing Plasmodium falciparum resistance to SP has challenged the effectiveness of this strategy. Resistance to SP is caused by point mutations in the genes encoding dihydrofolate reductase and dihydropteroate synthase. The reduction in IPTp-SP efficacy associated with increased SP resistance has prompted alternative approaches to be considered. Screen-and-treat approaches using artemisinin combination therapies have been evaluated but current rapid diagnostic tests (RDTs) failed to detect low-density parasitemia and occult placental malaria infection, leading to an increase in adverse outcomes compared to IPTp-SP. Therefore, the World Health Organization recommends IPTp-SP in regions with low SP resistance mutation prevalence. Enhanced detection of malaria parasites in pregnancy, coupled with detection of relevant resistance mutations, holds promise for successful and targeted treatment of individual pregnant women and would provide vital data to inform the best strategies for the population. Innovative and user-friendly digital molecular diagnostic platforms, demonstrating the sensitivity of polymerase chain reaction (PCR), have emerged as valuable point-of-care tools. Among these, "Lacewing," developed by Imperial College London in collaboration with various partners, uses interchangeable diagnostic chip cartridges to conduct loop-mediated isothermal amplification reactions for detecting the pathogen's nucleic acid. In light of these developments, this study aims to evaluate the safety and efficacy of a hybrid strategy combining screening and treatment with RDT and dihydroartemisinin-piperaquine at the initial antenatal care visit, alongside standard IPTp-SP, to reduce the incidence of malaria in pregnancy as the primary outcome, in a high-transmission area of northern Zambia. Expanding upon this initiative, the study plans to recruit additional participants to assess the effectiveness of this hybrid approach

in reducing the occurrence of LBW as the coprimary outcome. Concurrently, it aims to evaluate Lacewing's performance in detecting malaria in pregnancy and identifying mutations associated with SP resistance. The study includes a descriptive cross-sectional survey to delve into contextual factors, community perceptions, needs, lived experiences, or user stories regarding malaria diagnosis and treatment, and digital molecular diagnostics use.

Who can participate?
Pregnant women aged at least 15 years old with a gestational age of 16 to 26 weeks at enrolment

What does the study involve?
Interventional:
In this study, two methods for preventing malaria in pregnant women will be compared. Upon their first Antenatal Care Visit, one group will receive the standard malaria in pregnancy (MIP) chemoprevention protocol involving sulfadoxine-pyrimethamine (IPTp-SP). The other group will undergo the standard MIP chemoprevention alongside an additional diagnostic test using RDT /Microscopy. If the test results are negative, they will be treated with SP, while if positive, they will receive a different medication called dihydroartemisinin-piperaquine (DP). Furthermore, mothers in both groups will be screened using a tool named Lacewing, in addition to RDT /Microscopy. The effectiveness of the Lacewing tool will be evaluated in comparison to PCR, including RDT/Microscopy. Both groups will continue to receive regular doses of SP until delivery.

Observational:
Data will be systematically gathered to explore the perceptions and experiences surrounding malaria diagnosis and treatment. This will entail conducting interviews, facilitating focus group discussions, making observations, and recording field notes. The insights gleaned from this data collection process will serve to shape the design of the subsequent phase of the study.

What are the possible benefits and risks of participating?
Mothers enrolled in this trial will receive specialized care accessible every day, including weekends, if they experience any health concerns. Furthermore, the insights gained from this study will not only benefit mothers and their offspring within the study area but also those residing in other malaria-endemic regions of Zambia and beyond. It is important to note that participation in this study carries certain risks. These may include discomfort from needle sticks, bruising, or the possibility of skin infection during blood collection. Additionally, there is a slight risk associated with medication intake for the baby. However, these drugs are recommended for pregnant women in their second and third trimesters, deemed safe, albeit with potentially unknown risks.

Where is the study run from?
Tropical Diseases Research Centre (TDRC) (Zambia)

When is the study starting and how long is it expected to run for?
September 2023 to July 2025

Who is funding the study?
The National Institute of Health and Care Research (NIHR) through Imperial College (UK)

Who is the main contact?
Dr Jean-Bertin Bukasa Kabuya, kabuyaj@tdrc.org.zm

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Dr Jean-Bertin Bukasa Kabuya

ORCID ID
https://orcid.org/0000-0003-0339-9101

Contact details
Feira 1, Kansenshi
Ndola
Zambia
10101
+260 0977338641
kabuyaj@tdrc.org.zm

Additional identifiers

Protocol serial number
TDRC/09/2023

Study information

Scientific Title
A Hybrid of Screen-and-Treat and Intermittent Presumptive Therapy for the Prevention of Low Birth Weight in Malaria in Pregnancy in the context of parasite resistance to sulphadoxine-pyrimethamine in a malaria high transmission area of Nchelenge in Zambia

Acronym
DIDA-MALAPREG

Study objectives
Combining screen-and-treat during initial antenatal care (ANC) with intermittent Presumptive Treatment in Pregnancy using Sulfadoxine-pyrimethamine (IPTp-SP) could enhance the efficacy of IPTp-SP in managing and preventing malaria during pregnancy, thereby mitigating associated adverse outcomes. Enhanced detection of malaria parasites in pregnancy, coupled with detection of relevant resistance mutations, would allow successful and targeted treatment of individual pregnant women and provide vital data to inform the best strategies for the population.

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 11/11/2023, National Health Research Ethics Board (NHREB) (Chalala Office Lot No. 18961/M, Off Kasama Road, P.O. Box 30075., Lusaka, 10101, Zambia; +260211 250309; znhrasec@nhra.org.zm), ref: NHREB001/01/11/2023

Study design
Phase IIIb open-label randomized controlled superiority trial with a descriptive cross-sectional survey

Primary study design
Interventional

Study type(s)
Diagnostic, Other, Prevention, Screening, Treatment, Safety, Efficacy

Health condition(s) or problem(s) studied
Malaria diagnostic and prevention in pregnant women

Interventions
This study has both interventional and observational elements as follows:
Interventional:
The study is a phase IIIb open-label randomized controlled superiority trial of standard intermittent Presumptive Treatment in Pregnancy using Sulfadoxine-pyrimethamine (IPTp-SP) versus IPTp-SP plus screen-and-treat using Dihydroartemisinin-Piperaquine (DP) while also assessing the performance of a molecular digital diagnostic tool called the Lacewing.

Observational:
Descriptive cross-sectional survey.

Interventional:
Participants randomized to the IPTp-SP arm will receive care according to current national guidelines. Participants randomized to the IPTp-SP plus screen-and-treat using DP (IPTp-SP+) arm will receive standard-of-care with the addition of screen-and-treat using Rapid Diagnostic Tests (RDT)/microscopy and DP at the first ANC visit.
The diagnostic accuracy of Lacewing will be evaluated by comparing it against PCR, and commonly utilized comparator tests including microscopy and RDT, using established metrics of diagnostic performance. Treatment allocation will be determined based on the results obtained from the comparator tests.
Participants allocated to the IPTp-SP+ group who test positive by RDT and/or microscopy during their first ANC visit will receive a complete treatment course of DP (40 mg Dihydroartemisinin/ 320 mg piperaquine), consisting of three tablets daily for three days. All other participants, including those in the IPTp-SP+ arm with a negative RDT result, will be administered SP during their initial visit. Subsequently, participants in both groups will receive monthly doses of SP during follow-up visits until delivery. SP dosage will adhere to national guidelines, with one dose comprising 1500 mg sulfadoxine and 75 mg pyrimethamine, administered at intervals of no less than 4 weeks between doses.

Observational:
Qualitative data will be collected to explore the contextual factors, community perception, needs, lived experiences or user stories about malaria diagnosis and treatment as well as the use of digital molecular diagnostics. In addition, qualitative data will also be used to generate

themes and questions for the quantitative strand in the second phase. Semi-structured interview guides, Focus Group Discussions (FGD), observations and field notes, will be used to collect the qualitative data.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine, Lacewing molecular digital diagnostic tool

Primary outcome(s)
Mean birth weight and prevalence of low birth weight (LBW) newborns measured using data collected in patient records at the end of the study period

Key secondary outcome(s))
1. Medication-related adverse events and serious adverse measured using data collected in patient records at the end of the study period
2. Sensitivity and Specificity including the proportion of SP resistance mutation as determined by Lacewing measured by comparing it against PCR at the end of the study period
3. Proportions of preterm delivery measured using data collected in patient records at the end of the study period
4. The proportion of stillbirths measured using data collected in patient records at the end of the study period
5. The proportion of congenital malaria cases measured using data collected in patient records at the end of the study period
6. The proportion of maternal anemia measured using data collected in patient records at the end of the study period
7. The incidences of neonatal deaths measured using data collected in patient records at the end of the study period
8. The proportions of malaria at delivery measured using data collected in patient records at the end of the study period
9. The positive and negative predictive values measured using data collected in patient records at the end of the study period

Completion date
31/07/2025

Eligibility

Key inclusion criteria
1. Gestational age of 16 to 26 weeks at enrolment
2. Asymptomatic* on presentation
3. Hb ≥ 7 g/dL
4. HIV negative at enrolment
5. No history of IPTp-SP or antimalarial drug use during the current pregnancy
6. At least 15 years old
7. Residence within the health facility catchment area

8. Willing to deliver at the health facility
9. Willing to adhere to the study requirements (HIV voluntary counseling and testing (VCT included)
10. Ability to provide written informed consent; if the woman is a minor of age/not emancipated, the consent must be given by a parent or legal guardian according to national law

(* Asymptomatic defined as the absence of fever (temperature <37.5 °C) at baseline; less than three of the following symptoms: fever in the past 24 h, weakness/fatigue; muscle and/or joint aches, headache. An assent will also be obtained from the participant).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
15 years

Sex
Female

Key exclusion criteria
1. HIV positive or unknown at enrolment
2. Hb<7 g/dl
3. History of allergic reactions to the study drugs
4. History of known pregnancy complications or bad obstetric history including pre-existing illness likely to cause complication of pregnancy such as repeated abortions, stillbirths or eclampsia
5. History or presence of major illnesses likely to influence pregnancy outcome including hypertension, diabetes mellitus, asthma, epilepsy, renal disease, liver disease, fistula repair, heart disease, or active tuberculosis
6. Current cotrimoxazole prophylaxis or ARV treatment
7. Any significant illness at the time of screening that requires hospitalization, including severe malaria
8. Intent to move out of the study catchment area before delivery or deliver at relative's home out of the catchment area
9. Prior enrolment in the study or concurrent enrolment in another study
10. Unable to take oral medication
11. Clear evidence of recent (2 weeks) treatment with antimicrobials with antimalarial activity (clindamycin, azithromycin, clarithromycin, levofloxacin etc.)
12. On at least one of the following drugs: Pentamidine, Antiarrhythmic agents (e.g., amiodarone, sotalol), Antihistamines (e.g., promethazine), Antifungals (systemic): ketoconazole, fluconazole, itraconazole, Diuretics (e.g., hydrochlorothiazide, furosemide), Antipsychotics (neuroleptics): haloperidol, thioridazine, Antidepressants: imipramine, citalopram, escitalopram, Antiemetics: domperidone, chlorpromazine, ondansetron

Date of first enrolment

13/05/2024

Date of final enrolment
31/01/2025

Locations

Countries of recruitment
Zambia

Study participating centre
Nchelenge
Nchelenge district
Luapula
Zambia
10101

Sponsor information

Organisation
Tropical Diseases Research Centre

ROR
https://ror.org/03y122s09

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request at the time of publication from Dr Jean-Bertin Bukasa Kabuya, kabuyaj@tdrc.org.zm. De-identified data from this study will be deposited on the Zenodo platform at http://zenodo.org. The type of data stored will be a fully analysable and cleaned primary de-identified data set. Keywords will be provided to scientists upon reasonable request and after agreement by the TDRC directorate. Consent from participants was required and obtained. Only de-identified data will be shared.

IPD sharing plan summary
Stored in publicly available repository, Available on request