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Assessing how good a single and low dose of primaquine is at stopping the transmission of falciparum malaria between children and mosquitoes and how primaquine is handled by the body

Submission date 09/07/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 26/07/2021	**Overall study status** Completed	
Last Edited 08/10/2025	**Condition category** Infections and Infestations	

Plain English summary of protocol

Background and study aims

Plasmodium falciparum malaria is a parasitic infection transmitted by mosquitoes that causes 400,000 deaths per year, mostly in African children. To complete its life cycle, mosquitoes take up mature male and female forms (gametocytes) from human blood, which mate to produce oocysts. Primaquine is the only drug that kills mature gametocytes. The aim of this study is to assess the effectiveness of a single low dose of pediatric primaquine in children with acute uncomplicated falciparum malaria, adapting the WHO-recommended adult dose (0.25 mg/kg).

Who can participate?

Young children aged 6 months to 5 years with acute uncomplicated Plasmodium falciparum malaria

What does the study involve?

Participants are randomly allocated to receive the standard treatment (artesunate pyronaridine) alone or with primaquine. How well primaquine blocks transmission is assessed by feeding mosquitoes on blood samples and seeing if oocysts are present (failure) or absent (success). By measuring primaquine concentrations, the researchers will see if primaquine is affected by standard treatment.

What are the possible benefits and risks of participating?

Primaquine is generally well tolerated. The main side effects are abdominal pain which is dose-related and improved by taking PQ with food.

The most important side effect is acute hemolytic anaemia (destruction of red blood cells) in individuals with G6PD deficiency (a genetic disorder). Its severity is related to the degree of G6PD deficiency and the primaquine dose. Haemolysis is less severe in the African (A-) G6PD variant compared to the Asian and Mediterranean variants and lower doses of primaquine are

used in this study.
Artesunate pyronaridine is usually well tolerated with few patients needing to be withdrawn because of gastrointestinal (digestive system) toxicity. Raised alanine aminotransferase (ALT) and raised bilirubin have been reported but repeat dose studies have not been associated with clinically significant toxicity. The repeated treatments with pyronaridine-artesunate did not increase the specific risks of liver injury. This led to the lifting of the registration label that restricted its use to once only. Hepatotoxicity events (liver damage) with pyronaridine–artesunate were more common in adults than in children younger than 5 years or aged 5 to younger than 18 years, and more common in patients weighing at least 20 kg than in patients less than 20 kg. In a repeated treatment study conducted in Burkina Faso, Mali and Guinea, none of the hepatotoxicity events were associated with any signs or symptoms, required any intervention, or resulted in any consequences. The researchers will monitor patients to detect possible early drug-induced hepatotoxicity.
Blood taking causes discomfort but this tends to be brief. Rarely, a venepuncture or finger stick site may become infected. Full aseptic techniques will be used when taking blood to minimise the infection risk.
Patients who enrol into this study will benefit from the close follow-up by the study doctors of their malaria episode and any other minor illnesses that occur during the follow-up period. Adding primaquine to treatment of malaria and the information obtained will benefit the wider community because if scaled up, primaquine should result in a further reduction in malaria transmission. The patient will be fully taken in charge of by the study for the period of admission in the health centre and money will provided to pay for transport for the follow-up visits. No other payments will be made. The researchers will compensate legal guardians for their time; this will be 5000 FCFA/day (about 7 pounds sterling). Reasonable transport costs will also be reimbursed for caregivers attending follow-up visits.

Where is the study run from?
Groupe de Recherche Action en Santé (GRAS) (Burkina Faso)

When is the study starting and how long is it expected to run for?
September 2020 to October 2025

Who is funding the study?
European & Developing Countries Clinical Trials Partnership (EDCTP)

Who is the main contact?
Bob Taylor
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
MAL21003, Grant reference: RIA2019PD-2893

Study information

Scientific Title
The anti-infectivity efficacy and pharmacokinetics of WHO-recommended single low dose primaquine in children with acute Plasmodium falciparum

Acronym
SLDPQ-BF

Study objectives
The key hypothesis to be tested is whether single low dose primaquine will enhance transmission blocking in children <5 years.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 29/07/2021, Oxford Tropical Research Ethics Committee (University of Oxford, Research Services, University Offices, Wellington Square, Oxford OX1 2JD, UK; +44 (0)1865 (2) 82106; oxtrec@admin.ox.ac.uk), ref: 13-21
2. Approved 01/07/2022, Ethics Committee for Health Research (03 BP 7009, Ouagadougou 03, Burkina Faso, West Africa; +226 70 26 89 98; email not provided), ref: 2022-06-149

Study design
Randomized open-label study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute uncomplicated Plasmodium falciparum malaria

Interventions
Current intervention as of 28/06/2022:
Anti-infectivity study
This is an open, randomised, parallel, phase IIb trial assessing the anti-infectivity efficacy, tolerability and PK of single low-dose primaquine (SLDPQ) in paediatric patients from Burkina Faso with acute uncomplicated Plasmodium falciparum malaria. Infectivity will be assessed by direct membrane feeding assays (D0, D1, D2, and D7).

A computer-generated randomisation list will be provided. The treatment allocation will be placed in a sealed opaque envelope which will be opened after a study (randomisation) number is given. The treatment allocation will describe the treatment arm.

There will be two arms and patients will be randomised to receive either:
1. Artesunate pyronaridine (ASPYR), dosed by weight. ASPYR granules will be used for patients weighing between 5-20 kg; thereafter, tablets will be used
2. ASPYR + SLDPQ (allometrically scaled weight-based regimen)

Acceptability study
This will be done using the ClinSearch Acceptability Score Test (CAST®) and then calculating the score.

Qualitative studies
KAP survey
A knowledge, attitudes and practice (KAP) survey on malaria and health-seeking behaviour will be conducted. This will consist of a list of mostly simple yes/no questions about malaria, like how commonly affected people are, its dangers, what families do when there is a fever in the family, do they take all the prescribed drugs, are drugs kept for other children. The researchers will also collect basic economic data, including willingness to pay, household income, cost of visiting the clinic, loss of work days.

Focus group discussions
Focus group discussions on broader issues will include e.g. drug adherence, how to improve it, monitoring side effects in the community, using a drug like primaquine that aims to improve health in the community rather than the individual benefit. There is no fixed sample size but the researchers plan for between 8 to 12 mothers/legal guardians. The process will be explained to mothers/legal guardians when informed consent is taken. The researchers will aim for sessions lasting 60 minutes but mothers can leave early if they feel they have had enough.

The discussion will be focused on the following topics:
1. General knowledge about malaria
2. Home management of fevers/treatment-seeking behaviour
3. Practice against malaria assessment questions
4. Drug (primaquine) adherence and ways to improve this
5. Perceptions on the use of tablets vs. granules
6. Improving health in the community with the use of drugs that have community rather than an individual benefit
7. Willingness to pay

All conversations are regarded as confidential and any note-taking will not include names and only first names will be used. The discussions will be recorded. Both will be kept securely locked with limited access to the original notes/recordings and the data in the database. At the study end, notes and recordings will be destroyed. Participants will be told that anonymised data may be shared with other researchers and some of their quotes used in presentations.

Previous intervention:
Anti-infectivity study
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Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Artesunate pyronaridine, primaquine

Primary outcome(s)
Current primary outcome measure as of 28/06/2022:
1. Proportions of patients infecting ≥1 mosquito in the ASPYR arm vs ASPYR+SLDPQ arm assessed by direct membrane feeding on days 0, 1, 2, and 7
2. Mean within-person percentage change in mosquito infectivity assessed by direct membrane feeding at baseline and on days 1, 2, 7, and 14

Previous primary outcome measure:
1. Proportions of patients infecting ≥1 mosquito in the ASPYR arm vs ASPYR+SLDPQ arm assessed by direct membrane feeding at days 2, 3, 7 and 14
2. Mean within-person percentage change in mosquito infectivity assessed by direct membrane feeding on days 2, 3, 7 and 14 vs baseline

Key secondary outcome(s))
Current secondary outcome measures as of 28/06/2022:
1. Determine mosquito infectivity by measuring proportion of mosquitoes with detected oocysts and sporozoites, oocyst intensity & sporozoite index on days 0, 1, 2, and 7

2. Gametocyte carriage assessed by quantitative nucleic acid sequence-based amplification and microscopy on days 0, 1, 2, 7, and 14
3. Primaquine exposure and anti-infectivity efficacy measured using pharmacokinetics (PK) on days 0 and 1 and direct membrane feeding assay (DMFA) on days 0, 1, 2, and 7
4. Haemoglobin (Hb) dynamics & recovery by Day 28 measured using a HemoCue® machine on days 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42
5. Presence of sickle cell trait/disease, thalassemia and G6PD variants measured using PCR on day 0
6. Cure rate measured using microscopy of a Giemsa stained thick blood film on day 42
7. Parasite and fever clearance times measured using microscopy and a thermometer respectively on days 0, 1, 2, 3, 7, 14, 21, 28, 35 and 42
8. Tolerability measured using adverse events, methaemoglobin oximeter on day 0, 1, 2, 3, 7, 14, 21, 28, 35, and 42 and biochemistry on days 0 and 7
9. CYP 2D6 polymorphisms measured using PCR on day 0
10. PQ and carboxyPQ PK parameters measured using PK on days 0 and 1
11. Covariates explaining variability in PQ and carboxyPQ PK parameters measured using nonlinear mixed-effects modelling on days 0 and 1
12. Acceptability score measured using the ClinSearch Acceptability Score Test (CAST) on day 0
13. Proportions of patients/careers responding to specific questions on a Knowledge, Attitude and Practices (KAP) questionnaire and the mean values of household income on day 0

Previous secondary outcome measures:
1. Gametocyte carriage assessed by quantitative nucleic acid sequence-based amplification and microscopy at days 0, 3, 7, 14, 28, 35 and 42
2. Primaquine exposure and anti-infectivity efficacy measured using pharmacokinetics (PK) and direct membrane feeding assay (DMFA) at days 0, 1 and days 0, 2, 3, 7 and 14, respectively
3. Haemoglobin (Hb) dynamics & recovery by Day 28 measured using a HemoCue® machine at days 0, 1, 2, 3, 7, 14, 21, 28, 35 and 42
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Completion date
04/08/2025

Eligibility

Key inclusion criteria
1. Participant parent/legal guardian is willing and able to give informed consent for participation in the study

2. Aged ≥6 months and <5 years
3. Weight ≥5 kg
4. Presentation with fever (axillary ≥37.5°C, tympanic ≥38°C) or fever history ≤24 h and clinically uncomplicated disease
5. P. falciparum parasitaemia 1,000 – 250,000/µl (mono-/mixed Plasmodium species) detected by light microscopy
6. Ability and willingness to comply with the protocol for the duration of the study and to comply with the study visit schedule

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
6 months

Upper age limit
5 years

Sex
All

Total final enrolment
56

Key exclusion criteria
1. General danger signs in children under 5 years or signs of severe falciparum malaria according to the definitions of WHO (2000) e.g. prostration, respiratory distress, reduced consciousness
2. Persistent vomiting as given in the history of the current illness
3. P. falciparum (Pf) parasitaemia >250,000/µl (>5% parasitaemia)
4. Haemoglobin (Hb) <5 g/dl
5. Patients on treatment for a significant illness e.g. HIV/AIDS, TB, leprosy or currently taking a drug known to cause haemolysis in G6PDd
6. Known to be allergic to PQ or ASPYR
7. On regular medication, which might interfere with antimalarial pharmacokinetics
8. Antimalarials taken within the last 2 weeks
9. Having taken a herbal medicine within the last 4 weeks
10. Previous participation in a malaria vaccine trial
11. Previous enrolment in the current trial or current enrolment in another trial
12. Severe malnutrition – defined as a mid-upper arm circumference (MUAC) <115 mm
13. Febrile condition due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhoea with dehydration) or other known underlying chronic or severe diseases (e.g. cardiac, renal or hepatic diseases, HIV/AIDS)

Date of first enrolment
15/07/2024

Date of final enrolment
30/11/2024

Locations

Countries of recruitment
Burkina Faso

Study participating centre
Groupe de Recherche Action en Santé (GRAS)
06 BP 10248
Secteur 19, Somgandé
Ouagadougou
Burkina Faso
-

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research organisation

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)
Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership (EDCTP), The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
Data will be made available upon reasonable request and in accordance with the data-sharing policies of GRAS and Mahidol Oxford Tropical Medicine Research Unit (MORU).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		03/09/2024	04/09/2024	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes