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Controlled human malaria infection transmission model - Mali

Submission date
11/03/2022

Recruitment status
No longer recruiting

Registration date
14/03/2022

Overall study status
Completed

Last Edited
13/11/2025

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Malaria is a serious infection spread by mosquitoes. If it's not diagnosed and treated quickly, you can die from it. In addition to the direct clinical burden, malaria represents a significant economic burden to affected countries, most of which are low and middle income countries. Malaria is a disease that affects many people in Africa, including Mali. Malaria is caused by small germs, called parasites, that are carried by some mosquitoes. When a person is bitten by this kind of infected mosquito they get malaria. Most malaria infection causes mild symptoms such as fever or headache or sometimes no symptoms at all, but malaria can also be serious and kill men, women, and children. If a mosquito bites someone who is infected with malaria, it can carry the malaria parasites to someone else, causing them to become sick as well. If researchers can discover a safe vaccine that stops malaria being passed from one person to the next, it would be a very important thing for millions of people. This study aims at establishing a Controlled Human Malaria Infection Transmission Model. Such a model could accelerate transmission vaccine development significantly.

Who can participate?
Healthy participants, aged 18 to 50 years

What does the study involve?
In this study, we aim to simulate how malaria parasites are transmitted from people to mosquitoes. We will first infect a participant with malaria parasites by an injection directly into your vein using a sterile needle and a syringe. Once these parasites have grown sufficiently, we will allow uninfected mosquitoes to bite a participant, to see if the malaria parasites can be passed to these mosquitoes. In this study we will not test any malaria vaccine, but in the future we will use this method to test vaccines that stop humans passing malaria to mosquitoes.

What are the possible benefits and risks of participating?
BENEFITS:
You will not receive any direct benefit from being in this study. You will not receive a malaria vaccine. Your participation in this study is important to simulate how malaria parasites are transmitted from people to mosquitoes, so that in the future researchers can use this kind of study to test vaccines and drugs that prevent malaria parasites being passed on to other people.

The information we learn will help in the development of a vaccine to prevent transmission of malaria parasites, which would be used in Mali and in other parts of the world where malaria is a problem.

These are some of the risks and discomforts associated with the study.

Blood draws
• Can cause pain, bruising, bleeding, sometimes lightheadedness or fainting, and rarely infection. The frequency and amount of blood that will be required for this study should not put you at risk for anemia or compromise your overall health. The total amount of blood you will give during the entire study will be less than the amount that people can safely give in one go for blood donation.

Antimalarial medications
• All medicines used to treat malaria in this trial have an excellent safety record. Some common side effects for each of the drugs are listed below.
• Volunteers with known bad reactions to the medicines used in this study are not allowed to be in the study.

Piperaquine (PPQ)
• The most commonly reported side effects of PPQ include: headache, changes in the electrical activity of the heart, fast heartbeat, weakness and fever. Uncommon side effects include: loss of appetite, cough, nausea, vomiting, diarrhoea, abdominal pain, changes of heart rhythm, liver abnormalities, itching, muscle or joint ache, dizziness and fitting, but generally these effects do not require people to stop using the drug.

Artemether/lumefantrine (AL, Coartem)
• The most commonly reported side effects of AL include: headache, loss of appetite, dizziness, weakness, muscle pains, and joint pains, but generally these effects do not require people to stop using the drug.

Primaquine (PQ)
• The most commonly reported side effects of PQ include: nausea, vomiting, heartburn and stomach cramps. In some people use of high doses of PQ can cause a drop in levels of red blood cells, but at the dose used in this study this should not occur.

Experimental Malaria Infection
Injection of blood-stage parasites or sporozoites (PfSPZ Challenge)
• Reactions at the site of the injection may include pain, redness, itching, bruising, pain with moving the arm, small lumps, and/or swelling. Other side effects like fever, chills, upset stomach, vomiting, loss of appetite, headache, diarrhea, tiredness, and muscle or joint pain may also occur, even several weeks after injection. These symptoms may be severe and may require a medication such as paracetamol. Typically these symptoms go away after 1 dose of this kind of medicine. Some of these symptoms may be due to a mild malaria infection thus you will be evaluated promptly for diagnosis.
• Injection with blood-stage parasites may in theory cause your body to create an immune response against some other people's red blood cells. This risk is considered extremely low, and has in fact never yet been seen following parasite injection.
• With any injection of a study product there is a small chance that a sudden, severe allergic reaction can occur, which can cause death. This reaction can start by tongue swelling, feeling lightheaded, or having trouble breathing. Because of this, you will be watched carefully for at least 30 minutes.

Malaria infection
• You may develop symptoms of malaria infection. The most common symptoms of malaria infection include headache, tiredness, muscle aches, back pain, joint aches, generalized body aches, fever, sweats, and chills. Less common side effects include upset stomach, vomiting, diarrhea, abdominal discomfort, cough, and dizziness.
• Infection with malaria in this study is diagnosed early and we will treat you quickly if you develop symptoms of malaria or if the level of parasites in your blood becomes too high. Also you may also have symptoms of malaria after treatment has started.
• Because the malaria infection in this study is treated early, it probably does not cause any permanent damage to your organs or long term medical problems. However, malaria infection that is not treated can cause severe illness including possible kidney, liver and/or heart problems, seizures, coma and even death.
• In order to avoid complications of malaria, it is extremely important that you follow the recommendations of the study staff and complete all required study visits and take all the drugs.
• You cannot give malaria to others, but there is a small risk you could give malaria to mosquitoes that bite you. You will be required to sleep with a bed net every night when on study, and use insect repellant if directed.

Risks of specific interest
• Heart problems. There is no known specific heart risk for healthy volunteers receiving experimental malaria infection injected sporozoites (PfSPZ Challenge). Heart problems when individuals have clinical malaria are extremely rare but can happen. Due to a few individual reports of heart problems in study volunteers undergoing malaria infection by mosquito bite or blood-stage parasites, we will not include individuals with an existing heart problem. We will screen for heart problems by asking about your medical history and that of your direct family. We will also ask you about any symptoms of heart disease and perform an ECG on you.
• Liver problems. In some volunteers undergoing experimental malaria infection in Europe and Australia, blood tests have shown temporary liver abnormalities. We think these abnormalities are a normal response to malaria infection and treatment and they go away again by themselves. Such abnormalities are generally not seen in studies in Africa in volunteers who have previously had malaria. To be on the safe side, we will not include volunteers who are at risk of liver disease and we will check in your blood for signs of liver damage.
• Blood problems. One volunteer in Australia developed very low levels of white blood cells after experimental malaria infection. This was probably also a response to the malaria infection. It has not been seen in studies in Africa. If you have symptoms of malaria infection during the study we will check levels of your white and red blood cells.

Genetic testing
• There is the possible risk that we discover a genetic characteristic that may suggest a risk of disease for you or your family or that we discover undisclosed family relationships.

Other risks
• It is unknown if the experimental malaria infection may alter your response if you ever have malaria infection in the future. We will inform you of any significant health effects and serious side effects if they occur in other subjects.
• There may be side effects from the experimental malaria infection with blood-stage parasites or sporozoites (PfSPZ Challenge), even serious or life threatening risks that we do not yet know about. We will monitor you for all side effects including any new symptoms.

Where is the study run from?
University of Sciences, Techniques and Technologies of Bamako (USTTB) (Mali)

When is the study starting and how long is it expected to run for?
December 2021 to May 2023

Who is funding the study?
European and Developing Countries Clinical Trials Partnership (the Netherlands)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
2021/335/CE/USTTB

Study information

Scientific Title
Controlled Human Malaria Infection models for evaluation of Plasmodium falciparum transmission-blocking interventions in healthy Malian adults

Acronym
CHMI-Trans Mali

Study objectives

The primary aim of this project is to develop and optimise a CHMI-transmission model in Mali (CHMI-trans Mali), an area of intense seasonal malaria. Once developed we can utilize this model to accelerate the evaluation of transmission-blocking interventions, down selecting the most promising interventions for evaluation against naturally-acquired infections.

Primary objectives:
1. Primary safety objective: To evaluate the safety and tolerability of the CHMI-transmission model in healthy Malian adult participants inoculated intravenously with either sporozoites (PfSPZ Challenge) or asexual blood-stages of Plasmodium falciparum (IBSM Challenge).
2. Primary efficacy objective: To determine the prevalence and kinetics of gametocytemia in healthy Malian adult participants inoculated intravenously with either sporozoites (PfSPZ Challenge) or asexual blood-stages of Plasmodium falciparum (IBSM Challenge).

Secondary objectives:
1. To determine the prevalence and kinetics of parasitemia in healthy Malian adult participants inoculated intravenously with either sporozoites (PfSPZ Challenge) or asexual blood-stages of Plasmodium falciparum (IBSM Challenge).
2. To assess the infectiousness of participants to Anopheles mosquitoes through Direct Skin Feeding Assay (DFA) and/or Direct Membrane Feeding Assay (DMFA).

Exploratory Objectives:
1. To determine the optimal parameters for the CHMI-transmission model in this population (inoculum type and dose, and timing of mosquito feeds), based on parasite/gametocyte kinetics and provisional DFA/DMFA results
2. To determine the required sample size for a CHMI-transmission study to evaluate efficacy of transmission-blocking interventions.
3. To assess the dynamics of gametocyte commitment, maturation and gametocyte sex ratio.
4. To assess transmission reducing activity (TRA) of participants' sera at baseline in Standard Membrane Feeding Assays (SMFAs) and assess correlations with DFA/DMFA during CHMI-transmission model
5. To assess correlations between baseline markers of malaria-exposure and asexual and sexual stage immunity with parasite and gametocyte kinetics during the CHMI-transmission model
6. To analyse immune responses in participants inoculated intravenously with either sporozoites (PfSPZ Challenge) or asexual blood-stages of Plasmodium falciparum

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/12/2021, USTTB Ethics Committee (Faculty of Medicine and Odonto-Stomatology & Faculty of Pharmacy, University of Sciences, Techniques and Technologies of Bamako (USTTB), P.O. Box: 1805 Point G, Bamako, Mali; +223 2022 52 77; mdiakite@icermali.org), ref: 2021/335/CE /USTTB

Study design
Single center open label sporozoite and blood-stage challenge study

Primary study design
Interventional

Study type(s)

Prevention

Health condition(s) or problem(s) studied
Malaria transmission blocking vaccine development

Interventions
Current interventions as of 13/11/2025:

Single center, open label, sporozoite and blood-stage challenge study.
A maximum of 42 healthy participants, aged 18 to 50 years, will participate in the study.
A maximum of 42 participants will be recruited following screening. Participants will be assigned to one of the following study (sub-) cohorts.

Participants in Cohort 1 and 2 will undergo controlled human malaria infection (CHMI) through a standard blood-stage challenge with Pf-infected erythrocytes by intravenous injection.
Participants in Cohort 3 will undergo a CHMI through a standard sporozoite challenge with PfSPZ Challenge (NF54) by direct venous inoculation.
All cohorts include the potential for dose escalation, and in principle the dose will increase ~10 /20-fold between parts (A, B and where applicable C). The starting inoculum dose will be that which has proven to be safe in previous CHMI studies. For the QIMR blood-stage inoculums this is ~2,800 viable parasites in malaria-naïve participants. For PfSPZ Challenge this is 3,200 sporozoites both in malaria-naïve participants (clinical trials.gov: NCT01624961) and pre-exposed adults in Mali. Each cohort may also include a consolidatory part (D), using the most effective and safe dose determined in parts A-C. Parts A, B, (C) and D for each cohort will be conducted sequentially, a minimum of 14 days apart. Dose escalation within each cohort will proceed if the efficacy criterion (≥100 p/µL in all subjects before day 14) is not met in the preceding part of that cohort, and in the absence of protocol-defined safety signals up to day 14 (any subject with a grade 3 AE probably or definitely related to CHMI; and/or >2 subjects with a grade 2 AE probably or definitely related to CHMI; and/or any subject with an initial parasitemia ≥100p/µL). If any such safety signals are observed, a data and safety monitoring board (DSMB) meeting will be convened to determine if it is safe to continue with dose escalation in that cohort. If an efficacious dose is identified for a Cohort before completing the full dose escalation schedule, the Principal Investigator may elect to challenge the remaining participants in that cohort with that dose, or proceed to part D. Based on data from Parts A and/or B, an DSMB meeting may also be convened to adjust the dose escalation schedule outside of the planned 10-20 fold dose increases (up to maximally 100-fold dose escalation at each step). The Principal Investigator may moreover decide to not conduct further dose-escalation and/or consolidation within any individual cohort due to logistical constraints.
Treatment with piperaquine will be used when necessary to clear pathogenic asexual parasites whilst leaving gametocytes unaffected. Piperaquine treatment is critical to preserve viable gametocytes and allow assessment of transmission endpoints. Treatment with low dose piperaquine (T1, 480 mg) will be initiated when either; (a) parasitemia reaches 1000 p/µL (in line with other CHMI studies in Africa), or (b) if a participant develops signs or symptoms of malaria accompanied by a positive thick-film blood smear (TBS). The initial clearance of parasitemia will be carefully monitored using daily blood samples. If recrudescent asexual parasitemia develops ≥1000 p/µL, a second, higher dose of piperaquine (T2, 960mg) will be administered. These treatment regimens cure asexual parasitemia while leaving immature and mature gametocytes unaffected. Clinical decisions will be based on duplicate microscopy readings. Venous blood samples will be collected for Direct Membrane Feeding Assays (DMFAs) and/or to Direct Skin Feeding Assays (DFAs) per MRTC SOPs on up to 3 occasions, the exact time-point being based on the density of gametocytemia as measured by gametocyte qRT-PCR and/or microscopy. These

assays will provide evidence of the infectivity of participants to mosquitoes at these time-points. At the end of study (day 49), or if a second recrudescence of asexual parasitemia develops >1000 p/µL, or if there is a safety concern or adverse event that in the opinion of the safety monitor or investigator requires immediate curative antimalarial treatment, participants will receive end of study treatment (T3, artemether/ lumefantrine and low-dose primaquine) to ensure they are parasite and gametocyte free.

Participants will be confirmed parasite free 1 to 3 days before challenge by qPCR and assessed again on the day of challenge. The challenge study will take place in a setting (season, location and accommodation) designed to minimise exposure to environmental mosquitoes and participants will be required to remain in the study area for the duration of CHMI follow-up.

In case a participant remains parasite negative by TBS for 21 days after challenge, frequency of follow-up visits will be reduced to ~3x/week. For those remaining negative by PCR until 28 days after challenge, end of the study treatment will be given and end of study will apply for that participant.

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Previous interventions:

Single center, open label, sporozoite and blood-stage challenge study.
A maximum of 42 healthy male participants, aged 18 to 50 years, will participate in the study.
A maximum of 42 participants will be recruited following screening. Participants will be assigned to one of the following study (sub-) cohorts.

Participants in Cohort 1 and 2 will undergo controlled human malaria infection (CHMI) through a standard blood-stage challenge with Pf-infected erythrocytes by intravenous injection.
Participants in Cohort 3 will undergo a CHMI through a standard sporozoite challenge with PfSPZ Challenge (NF54) by direct venous inoculation.
All cohorts include the potential for dose escalation, and in principle the dose will increase ~10 /20-fold between parts (A, B and where applicable C). The starting inoculum dose will be that which has proven to be safe in previous CHMI studies. For the QIMR blood-stage inoculums this is ~2,800 viable parasites in malaria-naïve participants. For PfSPZ Challenge this is 3,200 sporozoites both in malaria-naïve participants (clinical trials.gov: NCT01624961) and pre-exposed adults in Mali. Each cohort may also include a consolidatory part (D), using the most effective and safe dose determined in parts A-C. Parts A, B, (C) and D for each cohort will be conducted sequentially, a minimum of 14 days apart. Dose escalation within each cohort will proceed if the efficacy criterion (≥100 p/µL in all subjects before day 14) is not met in the preceding part of that cohort, and in the absence of protocol-defined safety signals up to day 14 (any subject with a grade 3 AE probably or definitely related to CHMI; and/or >2 subjects with a grade 2 AE probably or definitely related to CHMI; and/or any subject with an initial parasitemia ≥100p/µL). If any such safety signals are observed, a data and safety monitoring board (DSMB) meeting will be convened to determine if it is safe to continue with dose escalation in that cohort. If an efficacious dose is identified for a Cohort before completing the full dose escalation schedule, the Principal Investigator may elect to challenge the remaining participants in that cohort with that dose, or proceed to part D. Based on data from Parts A and/or B, an DSMB meeting may also be convened to adjust the dose escalation schedule outside of the planned 10-20 fold dose increases (up to maximally 100-fold dose escalation at each step). The Principal Investigator may moreover decide to not conduct further dose-escalation and/or consolidation within any individual cohort due to logistical constraints.
Treatment with piperaquine will be used when necessary to clear pathogenic asexual parasites

whilst leaving gametocytes unaffected. Piperaquine treatment is critical to preserve viable gametocytes and allow assessment of transmission endpoints. Treatment with low dose piperaquine (T1, 480 mg) will be initiated when either; (a) parasitemia reaches 1000 p/µL (in line with other CHMI studies in Africa), or (b) if a participant develops signs or symptoms of malaria accompanied by a positive thick-film blood smear (TBS). The initial clearance of parasitemia will be carefully monitored using daily blood samples. If recrudescent asexual parasitemia develops ≥1000 p/µL, a second, higher dose of piperaquine (T2, 960mg) will be administered. These treatment regimens cure asexual parasitemia while leaving immature and mature gametocytes unaffected. Clinical decisions will be based on duplicate microscopy readings. Venous blood samples will be collected for Direct Membrane Feeding Assays (DMFAs) and/or to Direct Skin Feeding Assays (DFAs) per MRTC SOPs on up to 3 occasions, the exact time-point being based on the density of gametocytemia as measured by gametocyte qRT-PCR and/or microscopy. These assays will provide evidence of the infectivity of participants to mosquitoes at these time-points. At the end of study (day 49), or if a second recrudescence of asexual parasitemia develops >1000 p/µL, or if there is a safety concern or adverse event that in the opinion of the safety monitor or investigator requires immediate curative antimalarial treatment, participants will receive end of study treatment (T3, artemether/ lumefantrine and low-dose primaquine) to ensure they are parasite and gametocyte free.

Participants will be confirmed parasite free 1 to 3 days before challenge by qPCR and assessed again on the day of challenge. The challenge study will take place in a setting (season, location and accommodation) designed to minimise exposure to environmental mosquitoes and participants will be required to remain in the study area for the duration of CHMI follow-up.

In case a participant remains parasite negative by TBS for 21 days after challenge, frequency of follow-up visits will be reduced to ~3x/week. For those remaining negative by PCR until 28 days after challenge, end of the study treatment will be given and end of study will apply for that participant.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Controlled human malaria infection transmission model

Primary outcome(s)
Measured during the study visits. The number of visits will vary, but a maximum of 45 visits are planned:
1. Frequency and severity of adverse events in the CHMI-transmission study participants in each cohort measured using clinical exams and or with laboratory procedures during the study visit
2. Prevalence and density of gametocytes as determined by qPCR and/or thick-film blood smear (TBS) microscopy by cohort

Key secondary outcome(s))
Measured during the study visits. The number of visits will vary, but a maximum of 45 visits are planned:
1. Prevalence and density of parasitemia as determined by qRT-PCR and/or TBS microscopy by cohort

2. Proportion of infected Anopheles mosquitoes following DFA/DMFA in each cohort measured by microscopy assessment of mercurochrome stained mosquito midguts
3. Intensity of oocyst infection in mosquitoes following DFA/DMFA in each cohort measured by microscopy assessment of mercurochrome stained mosquito midguts
4. The sample size required to evaluate the efficacy of transmission blocking interventions in this population determined through mathematical modeling of the parasite/gametocyte kinetics and DFA/DMFA results at the end of the study

Completion date
13/05/2023

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 13/11/2025:

1. Aged ≥18 and ≤50 years and in general good health.
2. Known long-term resident (more than 1 year) of Sotuba or surrounding area.
3. Participant has adequate understanding of the procedures of the study and is able and willing (in the investigator's opinion) to comply with all study requirements, including, but not limited to:
3.1. remaining in Sotuba during the challenge period, not travelling during the study period, and remaining reachable (24/7) by mobile telephone throughout the entire study period
3.2. available to attend all study visits, and willing to sleep in appropriate accommodation close to the trial center during part of the study (from day 5 post-infection until either (i) end of study, or (ii) day 28 if parasitemia does not develop before this time
3.3. refraining from blood donation throughout the study period and for a 6 week period thereafter
4. Females of childbearing potential must be willing to use reliable contraception from day of screening until end of study (EOS). A reliable method of birth control includes one of the following:
• licenced oral contraceptives
• Intrauterine or implantable device
Exceptions to required pregnancy prevention includes the following:
• Postmenopausal state: defined as no menses for 12 months without an alternative medical cause
• Surgical sterilization
• Sexual abstinence
5. Able to provide proof of identity to the satisfaction of the study clinician completing the enrolment process.
6. Willing to have blood samples stored for future research.
7. The participant has correctly answered ≥80% of the questions on the Study Comprehension Exam.

Previous key inclusion criteria:

1. Males aged ≥18 and ≤50 years and in general good health.
2. Known long-term resident (more than 1 year) of Sotuba or surrounding area.
3. Participant has adequate understanding of the procedures of the study and is able and willing

(in the investigator’s opinion) to comply with all study requirements, including, but not limited to:
3.1. remaining in Sotuba during the challenge period, not travelling during the study period, and remaining reachable (24/7) by mobile telephone throughout the entire study period
3.2. available to attend all study visits, and willing to sleep in appropriate accommodation close to the trial center during part of the study (from day 5 post-infection until either (i) end of study, or (ii) day 28 if parasitemia does not develop before this time
3.3. refraining from blood donation throughout the study period and for a 6 week period thereafter
4. Able to provide proof of identity to the satisfaction of the study clinician completing the enrolment process.
5. Willing to have blood samples stored for future research.
6. The participant has correctly answered ≥80% of the questions on the Study Comprehension Exam.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
Yes

Age group
Adult

Lower age limit
18 years

Upper age limit
50 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current key exclusion criteria as of 13/11/2025:

1. Pregnancy (as determined by a positive urine or serum beta human choriogonadotropin (β-hCG) test), lactation or intention to become pregnant during the study. (if female)
2. Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, such as cardiovascular, pulmonary, renal, hepatic, neurological, dermatological, endocrine, malignant, haematological, infectious, immunodeficient, psychiatric and other disorders, which could compromise the health of the participant during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following.
2.1. Body weight <50 kg or Body Mass Index (BMI) <18 or >30 kg/m2 at screening.
2.2. History, or evidence at screening, of elevated risk for cardiovascular disease, including arrhythmia or clinically relevant bradycardia, prolonged QT-interval (>450ms) or other relevant ECG abnormalities; a positive family history of cardiac events in 1st or 2nd degree relatives <50

years old, or of sudden (cardiac) death.
2.3. Severe asthma, defined as asthma that is unstable or required emergent care, urgent care, hospitalization, or intubation during the past 2 years, or that has required the use of oral or parenteral corticosteroids at any time during the past 2 years
2.4. History of a severe allergic reaction or anaphylaxis
2.5. Autoimmune or antibody-mediated disease including but not limited to: systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, or autoimmune thrombocytopenia
2.6. A medical history of functional asplenia, sickle cell disease, thalassaemia trait/disease or G6PD-deficiency.
2.7. History of epilepsy in the period of five years prior to study onset, even if no longer on medication.
2.8. Screening tests positive for Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV)
2.9. Hemoglobin, white blood cell (WBC), absolute neutrophil count, or platelet, alanine transaminase (ALT) or creatinine (Cr) levels outside the local laboratory–defined limits of normal. (Subjects may be included at the investigator's discretion for "not clinically significant" values outside of normal range and ≤ Grade 2.
2.10. Chronic use of immunosuppressive or other immune modifying drugs within three months prior to study onset (inhaled, intranasal and topical corticosteroids and oral anti-histamines exempted) or expected use of such during the study period.
2.11. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years.
2.12. Behavioral, cognitive, or psychiatric disease that in the opinion of the investigator affects the ability of the participant to understand and comply with the study protocol
2.13. Suspicion of alcohol or illicit drug abuse interfering with health or normal occupational or social function in the period of one year prior to study onset.
3. Any recent or current systemic therapy with an antibiotic or drug with potential anti-malarial activity (chloroquine, doxycycline, tetracycline, piperaquine, benzodiazepine, flunarizine, fluoxetine, tetracycline, azithromycin, clindamycin, erythromycin, hydroxychloroquine, etc.; allowable timeframe for use at the Investigator's discretion).
4. Previous receipt of any malaria vaccine unless approved by the Principal Investigator.
5. Receipt of any live (attenuated) vaccine within the past 4 weeks, or of any vaccine within the past 2 weeks of enrolment
6. Known hypersensitivity to or contra-indications (including co-medication) for use of piperaquine, artemether-lumefantrine, primaquine, latex or history of severe (allergic) reactions to mosquito bites.
7. Current use of any drug that is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
8. Current use of drugs that are known to prolong the QTc interval such as: antiarrhythmics of classes I and III; neuroleptics and antidepressant agents; certain antimicrobials including some macrolides, fluoroquinolones, pentamidine, saquinavir, imidazole, and triazole antifungal agents; certain non-sedating antihistaminics (terfenadine, astemizole); cisapride.
9. Use of immunoglobulin or blood products within 6 months prior to enrolment
10. Participation in any other clinical study, or receipt of any investigational product, in the 30 days prior to the start of the study or during the study period unless approved by the Principal Investigator.
11. Any other significant disease, disorder or finding which, in the opinion of the investigator, may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study or impair interpretation of the study data. In case participants are excluded due to diagnosis of a contra-indication during screening, the study will ensure and cover treatment for acute conditions and referral for chronic

conditions.
12. For cohort 1 and 2 (blood stage challenge): Known receipt of a blood transfusion in the past.
13. Female participants with blood type Rhesus (Rh)-c negative and/or (Rh)-e negative are excluded from participation in study groups receiving a blood-stage challenge with a dose exceeding 2,800 iRBC.

Previous key exclusion criteria:

1. Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, such as cardiovascular, pulmonary, renal, hepatic, neurological, dermatological, endocrine, malignant, haematological, infectious, immunodeficient, psychiatric and other disorders, which could compromise the health of the participant during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following.
1.1. Body weight <50 kg or Body Mass Index (BMI) <18 or >30 kg/m2 at screening.
1.2. History, or evidence at screening, of elevated risk for cardiovascular disease, including arrhythmia or clinically relevant bradycardia, prolonged QT-interval (>450ms) or other relevant ECG abnormalities; a positive family history of cardiac events in 1st or 2nd degree relatives <50 years old, or of sudden (cardiac) death.
1.3. Severe asthma, defined as asthma that is unstable or required emergent care, urgent care, hospitalization, or intubation during the past 2 years, or that has required the use of oral or parenteral corticosteroids at any time during the past 2 years
1.4. History of a severe allergic reaction or anaphylaxis
1.5. Autoimmune or antibody-mediated disease including but not limited to: systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren's syndrome, or autoimmune thrombocytopenia
1.6. A medical history of functional asplenia, sickle cell disease, thalassaemia trait/disease or G6PD-deficiency.
1.7. History of epilepsy in the period of five years prior to study onset, even if no longer on medication.
1.8. Screening tests positive for Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV)
1.9. Hemoglobin, white blood cell (WBC), absolute neutrophil count, or platelet, alanine transaminase (ALT) or creatinine (Cr) levels outside the local laboratory–defined limits of normal. (Subjects may be included at the investigator's discretion for "not clinically significant" values outside of normal range and ≤ Grade 2.
1.10. Chronic use of immunosuppressive or other immune modifying drugs within three months prior to study onset (inhaled, intranasal and topical corticosteroids and oral anti-histamines exempted) or expected use of such during the study period.
1.11. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years.
1.12. Behavioral, cognitive, or psychiatric disease that in the opinion of the investigator affects the ability of the participant to understand and comply with the study protocol
1.13. Suspicion of alcohol or illicit drug abuse interfering with health or normal occupational or social function in the period of one year prior to study onset.
2. Any recent or current systemic therapy with an antibiotic or drug with potential anti-malarial activity (chloroquine, doxycycline, tetracycline, piperaquine, benzodiazepine, flunarizine, fluoxetine, tetracycline, azithromycin, clindamycin, erythromycin, hydroxychloroquine, etc.; allowable timeframe for use at the Investigator's discretion).
3. Previous receipt of any malaria vaccine unless approved by the Principal Investigator.

4. Receipt of any live (attenuated) vaccine within the past 4 weeks, or of any vaccine within the past 2 weeks of enrolment
5. Known hypersensitivity to or contra-indications (including co-medication) for use of piperaquine, artemether-lumefantrine, primaquine, latex or history of severe (allergic) reactions to mosquito bites.
6. Current use of any drug that is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
7. Current use of drugs that are known to prolong the QTc interval such as: antiarrhythmics of classes I and III; neuroleptics and antidepressant agents; certain antimicrobials including some macrolides, fluoroquinolones, pentamidine, saquinavir, imidazole, and triazole antifungal agents; certain non-sedating antihistaminics (terfenadine, astemizole); cisapride.
8. Use of immunoglobulin or blood products within 6 months prior to enrolment
9. Participation in any other clinical study, or receipt of any investigational product, in the 30 days prior to the start of the study or during the study period unless approved by the Principal Investigator.
10. Any other significant disease, disorder or finding which, in the opinion of the investigator, may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study or impair interpretation of the study data. In case participants are excluded due to diagnosis of a contra-indication during screening, the study will ensure and cover treatment for acute conditions and referral for chronic conditions.
11. For cohort 1 and 2 (blood stage challenge): Known receipt of a blood transfusion in the past.

Date of first enrolment
03/05/2022

Date of final enrolment
21/03/2023

Locations

Countries of recruitment
Mali

Study participating centre
Malaria Research and Training Center (MRTC)
Faculty of Medicine and Odonto-Stomatology & Faculty of Pharmacy
University of Sciences, Techniques and Technologies of Bamako (USTTB)
P.O. Box: 1805 Point G
Bamako
Mali
BP 1805

Sponsor information

Organisation

Université des Sciences, des Techniques et des Technologies de Bamako

ROR
https://ror.org/023rbaw78

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
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2.0	17/02/2022	14/03/2022	No	Yes
Protocol file	version 2.0	17/02/2022	14/03/2022	No	No