Optimizing parasite transmission to laboratory-reared mosquitoes following controlled human malaria infection with Plasmodium vivax asexual blood stage parasites in malaria-naïve healthy volunteers in the Netherlands

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Main objective: Develop a protocol to reproducibly infect mosquitoes with blood from human study participants undergoing asexual blood stage CHMI with the P. vivax clone PvW1.Secondary objectives: Maximize mosquito infection rate with PvW1 by I)...

Ethical review	Approved WMO
Status	Completed
Health condition type	Infections - pathogen unspecified
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON57011

Source
ToetsingOnline

Brief title
RaViCHMI1

Condition

- Infections - pathogen unspecified

Synonym
Malaria

Research involving

Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Europese Unie

Intervention

- Product containing living (micro-) organisms or viruses

Keyword: controlled human malaria infection, malaria, Plasmodium vivax, transmission

Explanation

N.a.

Outcome measures

Primary outcome

Proportion of infected mosquitoes, measured as oocyst positivity, following
 exposure to blood of participants with P. vivax parasitaemia.

Secondary outcome

Number and severity of adverse events related to CHMI between inoculation and
 one week following antimalarial treatment

Study description

Background summary

Plasmodium vivax is the second-most important malaria parasite (following P. falciparum) and has a significant, although difficult to measure, disease burden, particularly in South and Southeast Asia as well as in South America. In parts of Africa, P. vivax infection also results in a significant health burden. The World Health Organization has therefore included the development of vaccines to prevent P. vivax malaria and transmission into its updated Malaria Vaccine Technology Roadmap. In order to assess the efficacy of malaria vaccine candidates, controlled human malaria infections (CHMI) play a pivotal role. This validated tool allows down-selection of vaccine candidates very early in clinical development based on the most relevant criterion - protective efficacy - with a minimal number of healthy and non-vulnerable participants. The gain in statistical power is achieved through highly controlled experimental conditions

with regards to the sample (e.g. similar background immunity, age and health status) and an inoculum that consistently leads to infection with similar kinetics. CHMI with P. falciparum is well established in the development pipeline for pre-erythrocytic, asexual blood stage and, since recently, also transmission-blocking vaccine candidates.
Today, P. falciparum CHMI is one of the most-used experimental models for vaccine development. In the past, intentional inoculation of humans with P. vivax were much more common. They have been used extensively in the first half of the 20th century for the treatment of late-stage syphilis (malariotherapy). It was considered a standard therapy and was experimentally used for other conditions; some until the second half of the 20th century. It is one of the first immune-therapies (the malaria-induced systemic inflammatory reaction was the therapeutic principle), had an estimated efficacy around 50% and was used in tens of thousands of patients (Snounou and Pérignon 2013). Until today, P. vivax CHMI plays a role in testing interventions, although the lack of standardised procedures and isolates as well as the scarcity of new interventions for P. vivax and difficulties in accessing well-defined challenge agents make them an underused technology.

In RaViCHMI1, a protocol for reproducibly infecting laboratory-reared mosquitoes following inoculation of healthy, adult, malaria-naïve participants with asexual blood stage parasites of the PvW1 clone of P. vivax will be established. This model will be used to 1) assess interventions that inhibit transmission to mosquitoes (e.g. transmission-blocking vaccines) and to 2) produce infected mosquitoes to assess interventions targeting the sporozoite and hepatic stages of the parasite life cycle.

Study objective

Main objective: Develop a protocol to reproducibly infect mosquitoes with blood from human study participants undergoing asexual blood stage CHMI with the P. vivax clone PvW1.
Secondary objectives: Maximize mosquito infection rate with PvW1 by I) using ex vivo gametocyte concentration techniques, and II) antimalarial treatment that minimizes malaria-associated symptoms and adverse events due to asexual parasitaemia while not affecting gametocyte viability during CHMI.

Study design

Single centre, sequential, non-controlled, non-randomized transmission study

Intervention

All participants undergo Controlled Human Malaria Iinfection with PvW1 and receive gametocyte-sparing and end-of-study antimalarial treatment.

Study burden and risks

Inoculum: Participants will undergo CHMI using a cryopreserved blood inoculum of the P. vivax clone PvW1. The inoculum has been produced from a prospectively screened and infected donor with a universal blood group who passes all criteria for blood donation. All procedures related to producing the blood inoculum were done under strict quality assurance. The inoculum has been used safely in 37 malaria-naïve participants in the UK, so far.
Malaria: The main risk of P. vivax malaria are symptoms of systemic inflammation, such as fatigue, fever, headache, and myalgia. It is commonly characterized as *benign tertian malaria* because, in contrast to P. falciparum malaria, the risk of complications in healthy adults with a recently acquired infection is extremely low. Nevertheless, there is a significant disease burden including complications and death, which are associated with chronic and relapsing infections, pregnancy, and co-morbidities. As a blood inoculum is used, there is no risk of P. vivax relapse. The antimalarial treatment is curative, therefore no complications of chronic or recurrent malaria may occur.
Antimalarial treatment: Participants will receive gametocyte-sparing antimalarial treatment with piperaquine or mepacrine as well as end-of-study treatment with atovaquone-proguanil or artemether-lumefantrine. All antimalarials have been given in millions of doses and their safety profile is well described. Piperaquine, mepacrine and lumefantrine can prolong the QT interval. Therefore, an electrocardiogram is part of screening. Potential participants with ECG abnormalities will be excluded.
Mosquito bites: Mosquito bites can cause local discomfort. Mild local inflammation and pruritus typically accompanies the bite of the insect. In contrast to other insect bites (e.g., bees) anaphylaxis after mosquito bites is extremely rare and has never been reported in CHMI studies.
Phlebotomy: Up to 40 phlebotomies will be done during the study: at screening, before inoculation, daily until treatment completion and at two late follow up visits. During CHMI, daily monitoring of parasitaemia will be done to initiate treatment and reduce potential symptoms of malaria. Phlebotomies will be performed by qualified nurses and physicians and sites of sampling will be frequently inspected. For blood sampling in short intervals an intravenous catheter may be used. No more than 500 mL of blood (the equivalent of one blood donation) will be sampled over the trial period.
Other burden and risks: Wild Anopheles mosquitoes may be infected by a participant. The risk is well below the background (imported infections from endemic areas) as gametocytes will circulate only shortly and at very low numbers. In addition, there are very few competent Anopheles species in the study area.
Benefits: There is no direct benefit for study subjects from participation in the trial. Subjects may indirectly benefit from general medical evaluation and health screening procedures. The group benefit of the study is mainly for people at risk for malaria; mostly in malaria-endemic regions but also travellers as RaViCHMI1 is intended to accelerate development of antimalarial

interventions.

Contacts

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Trial sites

Trial sites in the Netherlands

Radboud Universitair Medisch Centrum
Target size: 12

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

* Healthy, malaria-naïve volunteer aged 18-45 years.
* Able and willing (in the investigator*s opinion) to comply with all trial

requirements.
* General good health based on history and clinical examination.
* Written informed consent.

Exclusion criteria

* History of clinical malaria (any species).
* Any clinically significant abnormal finding on clinical examination or laboratory screening.
* Pregnancy, lactation or intention to become pregnant during the study period.

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Single
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-09-2024
Enrollment:	12
Duration:	2 months (per patient)
Type:	Actual

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Yes

Plan description
Alleen geanonimiseerde gegevens, op verzoek via Radboud data repository

Ethics review

Approved WMO Date:	10-09-2024
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2025
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-04-2025
Application type:	Amendment
Review commission:	CCMO

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL86484.091.24
Research portal	NL-005553