# Re-exposure of EHMI-8 human volunteers to live malaria sporozoites

Published: 15-10-2009
Last updated: 06-05-2024

Objectives: • Primary objective (parasitological): To explore the longevity of immunity against P. falciparum sporozoite challenge that was induced in the EHMI-8 study. • Secondary objective (immunological): To dissect mechanisms of protection and...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Protozoal infectious disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON33874

**Source**
ToetsingOnline

**Brief title**
EHMI-8B

### Condition

- Protozoal infectious disorders

**Synonym**
Malaria, plasmodium falciparum

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Sint Radboud
**Source(s) of monetary or material Support:** Stichting Dioraphte

## Intervention

**Keyword:** EHMI-8, malaria, plasmodium falciparum, re-exposure

## Outcome measures

### Primary outcome

Primary study parameters/endpoints:

• A significant difference in time of thick smear positivity between EHMI-8 and control volunteers

• A significant quantitative difference in parasitemia as measured by PCR between EHMI-8 and control volunteers

• A significant difference in kinetics of parasitemia between EHMI-8 and control volunteers as measured by PCR.

• A difference in occurrence of signs or symptoms between EHMI-8 and control volunteers

### Secondary outcome

Secondary study parameters/endpoints (immunological):

• Significant differences in immune response between EHMI-8 and control volunteers (including central and effector memory responses and regulatory T-cell reactivity)

• Significant differences in the outcome of in vitro functional growth and malaria stimulation assays between EHMI-8 and control volunteers

• Significant differences in cellular inflammatory pathways of antigen presenting cells

• The identification of antigens that correlate with protection and could be vaccine candidates

Exploratory endpoints (pathophysiological):

• To describe the effect of early malaria infection on (markers of) coagulation

• To describe the effect of early malaria infection on endothelial activation

• To describe the effect of early malaria infection on complement activation

• Significant differences in parasite VAR gene expression during infection

# Study description

### Background summary

Rationale: In the EHMI-8 study healthy Dutch volunteers were sterilely protected against P. falciparum challenge by repeated exposure to infected mosquitoes whilst under chloroquine prophylaxis. The surprisingly efficient induction of protection in this study strongly supports the development of whole parasite vaccines and is therefore an important finding to malaria vaccine development. In this study (EHMI8B) we would like to explore the longevity of the protective immune response and simultaneously further characterise immune mechanisms responsible for protection by re-exposing EHMI-8 volunteers to infected mosquito bites.

### Study objective

Objectives:
• Primary objective (parasitological): To explore the longevity of immunity against P. falciparum sporozoite challenge that was induced in the EHMI-8 study.
• Secondary objective (immunological): To dissect mechanisms of protection and identify correlates of protection.
• Exploratory objectives (pathophysiological): To explore the pathophysiology of early malarial infection, with specific attention to coagulation, endothelial activation, complement activation and VAR gene expression.

### Study design

Study design: single center, open label.

### Intervention

Intervention: All volunteers are expose to the bites of 5 Plasmodium falciparum infected mosquitoes. All volunteers will be treated similarly.

Study procedures: Volunteers that have previously participated in the EHMI-8 study and that have shown to be protected against the bites of infectious mosquitoes, will be re-exposed to the bites of infectious mosquitoes with live P. falciparum sporozoites. Five healthy volunteers will be recruited to serve as controls for the study procedures.
Criteria for treatment with a curative regimen of Malarone® (atovaquon/proguanil) are as follows:
• Positive thick smear on regular check-up
• Complaints of malarial infection and thick smear positive
• By decision of study doctor or the safety monitor
• On request of the volunteer
• On day 21 post challenge, if the volunteer has remained thick smear negative
Dosing will be as follows: once daily 4 tablets of 250/100mg, during three days, according to SWAB guidelines.

**Study burden and risks**

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Benefits: No benefit can be claimed for any of the volunteers. Even though volunteers might be protected to patent blood-stage P. falciparum in this re-challenge, these effects may not apply to field situations. Therefore, volunteers will be advised to take regular malaria prophylaxis when travelling to malaria endemic areas in the future.
Risks: Risks for volunteers are related to exposure to (early) P. falciparum malaria infection and side-effects of Malarone® treatment.
Burden: The study is associated with a short period (35 days) of intense clinical monitoring with frequent site visits (up to three times a day) and blood examinations. As it is unpredictable if and/or when subjects will develop a positive thick blood smear, it is impossible to state the exact number of site visits and blood examinations. However, the maximum number (in case a subject does not develop a positive blood smear) of site visits and blood examinations will be 43 with a maximum amount of collected blood of 500 mL. In addition periodical physical examinations will be performed and the subject is asked to complete a dairy.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Age > 18 and < 35 years healthy volunteers (males or females).
2. General good health based on history and clinical examination.
3. Negative pregnancy test.
4. Use of adequate contraception for females
5. All volunteers have to sign the informed consent form following proper understanding of the meaning and procedures of the study
6. Volunteer agrees to inform the general practitioner and agrees to sign a request for medical information concerning contra-indications for participation in the study
7. Willingness to undergo a P. falciparum sporozoite challenge
8. Resident near the RUNMC, Nijmegen or agree to stay in a hotel room during the intensive period of the study (Day 5 till Day T +3)
9. Reachable by mobile phone during the whole study period
10. Availability to attend all study visits
11. Agreement to refrain from blood donation to Sanquin or for other purposes, during the course of the study
12. Willingness to undergo an HIV, hepatitis B and C test
13. Negative urine toxicology screening test at screening visit and day before challenge

## Exclusion criteria

1. History of malaria other than participation in EHMI-8, or residence in malaria endemic areas within the past six months
2. Plans to travel to endemic malaria areas during the study period.
3. Only for newly recruited control volunteers: previous participation in any malaria vaccine study and/or positive serology for P. falciparum
4. Symptoms, physical signs and laboratory values suggestive of systemic disorders, including renal, hepatic, cardiovascular, pulmonary, skin, immunodeficiency, psychiatric and other conditions, which could interfere with the interpretation of the study results or compromise the health of the volunteers.
5. History of diabetes mellitus or cancer (except basal cell carcinoma of the skin)
6. History of arrhythmia*s or prolonged QT-interval
7. Positive family history in 1st and 2nd degree relatives of cardiac disease < 50 years old
8. An estimated, ten year risk of fatal cardiovascular disease of >=5%, as estimated by the Systematic Coronary Risk Evaluation (SCORE) system.
9. Any clinically significant deviation from the normal range in biochemistry or haematology blood tests or in urine analysis
10. Positive HIV, HBV or HCV tests
11. Participation in any other clinical study within 30 days prior to the onset of the study
12. Volunteers enrolled in any other clinical study during the study period
13. Pregnant or lactating women
14. Volunteers unable to give written informed consent
15. Volunteers unable to be closely followed for social, geographic or psychological reasons
16. Previous history of drug or alcohol abuse interfering with normal social function during a period of one year prior to enrolment in the study
17. A history of psychiatric disease
18. Known hypersensitivity for anti-malaria drugs
19. History of severe reactions or allergy to mosquito bites
20. The use of chronic immunosuppressive drugs, antibiotics, or other immune modifying drugs within three months before study onset (inhaled and topical corticosteroids are allowed) and during the study period
21. Contra-indications to Malarone® including treatment taken by the volunteers that interfere with Malarone®
22. Any confirmed or suspected immunosuppresive or immunodeficiency condition, including asplenia
23. Co-workers of the departments of Medical Microbiology or Internal Medicine of the Radboud University Nijmegen Medical Centre

# Study design

### Design

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| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Prevention |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 16-11-2009 |
| Enrollment: | 15 |
| Type: | Actual |

## Ethics review

Approved WMO

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| Date: | 15-10-2009 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

## 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 |
| --- | --- |
| ClinicalTrials.gov | NCT00757887 |
| CCMO | NL24193.091.09 |