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Plasmodium Sp. Sporozoites immunization of human volunteers

Submission date	Recruitment status	[_] Prospectively registered
04/04/2016	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
31/05/2016	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/07/2016	Infections and Infestations	

Plain English summary of protocol

Background and study aims
Malaria is a serious tropical disease that is spread by mosquitoes. It can be fatal if not diagnosed and treated quickly. Symptoms include fever, headache, sweats and chills, headaches, vomiting, muscle pain and diarrhoea. It is caused by an infection with a parasite called Plasmodium falciparum. It occurs when an infected mosquito bites a human and passes on the parasite into the bloodstream. There is evidence to suggest that malaria can be prevented via a vaccine using infected mosquitoes that that been irradiated but not killed. The radiation weakens the Plasmodium falciparum parasite, which is then taken from the insect and given to a patient in order to trigger an immune response and therefore immunity from malaria. This study looked at whether a minimum of 1,000 bites of irradiated Plasmodium falciparum-infected mosquitoes was safe and well tolerated and would result in 100% immunity from malaria.

Who can participate?
Healthy adults aged 18-50.

What does the study involve?
Participants are randomly allocated to one of three groups. Those in group 1 are assigned to the “true-immunized” group. They are immunized by the bites of mosquitoes infected with irradiated Plasmodium falciparum sporozoites, and then infected by malaria in a controlled way (controlled human malaria infection (CHMI)). Those in group 2 are assigned to the “mock-immunized” group. They are immunized by the bites of uninfected mosquitoes and not exposed to CHMI. Those in group 3 are assigned to the infectivity control group. They are not immunized but are exposed to CHMI at the same time as the true-immunized subjects in order to prove that infection occurs.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Naval Medical Research Center, Silver Spring (USA)

When is the study starting and how long is it expected to run for?
September 1999 to August 2003

Who is funding the study?
United States Military Infectious Diseases Research Program

Who is the main contact?
1. Dr Thomas Richie (scientific)
2. Dr Bradley Hickey (scientific)

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Prevention of malaria infection in healthy adults by bites of irradiated Plasmodium falciparum-infected mosquitoes: numbers and frequencies of bites and induction of sterile protection.

Study objectives
The primary goal is to duplicate the infection blocking protective immunity induced in humans by immunization with radiation-attenuated sporozoites. Thus, candidate vaccines, which are designed to induce the desired immune response against identified targets, must ultimately be transitioned into clinical trials in humans for assessment of immunogenicity and protective efficacy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Naval Medical Research Center Committee for Protection of Human Subjects, 09/12/1999, ref: NMRC.1999.0003 (DoD#30598)

Study design
Interventional non randomised trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Malaria infection

Interventions
Bites of irradiated Plasmodium falciparum-infected Anopheles stephensi mosquitoes delivered at different time intervals for a total of at least 1000 bites. Controls were mock-infected irradiated An. stephensi mosquitoes. All true and mock immunized subjects, and infectivity controls, will receive controlled human malaria infection (CHMI) delivered by bite of five P. flaciparum-infected mosquitoes.

Rolling recruitment took place at the NMRC Clinical Trials Center between September 1999 and August 2002. A total of 57 subjects were assessed for eligibility and 16 were excluded. The remaining 41 subjects, who met all screening criteria, were enrolled and assigned to the true-immunized (22 subjects), mock-immunized (13 subjects) and infectivity control (six subjects) groups. The group allocation was completed via convenience allocation and the controls (naïve subjects receiving controlled human malaria infection) were recruited and enrolled when needed prior to CHMI. Thirty of these 41 enrolled subjects initiated the immunization regimens (17 true-immunized, 13 mock-immunized), and three true-immunized underwent CHMI in 1999-2000 and seven true-immunized underwent CHMI in 2001-2002. Immunization was performed when PfRAS were available resulting in varying immunization schedules.

1. True-immunized group: Five subjects enrolled in 1999-2000 completed six immunizations and three subjects received CHMI in the first cohort in 2000. Ten of 14 subjects enrolled in 2001-2002 completed five immunizations, and seven of these 10 subjects completed six immunizations; six subjects who completed six immunizations and one subject who completed five immunizations (total seven subjects) received CHMI in the second cohort in 2002.
2. Mock-immunized group: In parallel to the true immunization group, seven subjects received at

least 5 mock immunizations over 175-239 days receiving a total of 1,210-1,890 irradiated non-infectious mosquito bites. None of these subjects underwent CHMI.
3. Control Group: Six participants were recruited for the control group (infectivity controls).

The CHMI procedure consisted of five non-irradiated mosquitoes, infected with the same NF54 strain of Pf used for immunization were allowed to feed once for five minutes on the subjects. All fed mosquitoes were dissected to determine the infectivity rate. Replacement mosquitoes for those of the initial five not feeding or feeding but found on dissection to have gland grades of 1 or less (10 sporozoites or less) were then allowed to feed and this process was repeated until five infectious bites had been achieved. Beginning seven days after CHMI, subjects were assembled each night in a regional hotel for clinical monitoring by study staff. Each morning, thick blood smears were made for microscopic examination, and sufficient passes over the slide were made using the high power objective such that approximately 40 µL of blood were examined. The presence of two parasites was required for a positive diagnosis, leading to immediate antimalarial treatment with chloroquine phosphate. The treatment regimen was directly observed and included 1000 mg chloroquine phosphate salt (600 mg chloroquine phosphate base) immediately, 500 mg salt (300 mg base) at 6 hours and again at 24 and 48 hours. Subjects who were positive were monitored daily by symptom checks and blood smears until three consecutive negative smears were documented, and subjects remaining negative were similarly monitored until day 21 post CHMI, then approximately every other day until day 28. Those remaining negative on day 28 were considered fully protected.

Intervention Type
Biological/Vaccine

Primary outcome(s)
Time to parasitemia: starting seven days after CHMI daily Giemsa-stained thick blood films from each subject, examined by microscopy for the presence of P. falciparum blood stage parasites. Symptomatic, undiagnosed subjects will have additional smears performed at the discretion of the study doctor, not to exceed one smear every 8-12 hours.

Key secondary outcome(s))
1. Safety and tolerability of immunization by 1,000 bites of irradiated Pf-infected mosquitoes after examination and verbal questioning of subjects for local adverse events on day of immunization and at 24, 48 and 72 hours and one and two weeks after each immunization
2. Correlates of protection by providing immune samples to measure immunological responses and the targeted Pf antigens two weeks after each immunization and prior to CHMI administered by bites of P. falciparum-infected mosquitoes

Completion date
01/08/2003

Eligibility

Key inclusion criteria
1. Healthy adults (male or non-pregnant female) 18-50 years of age or re-enrollees up to age 55 years
2. Available to participate for expected duration of an initial immunization series and challenge, for immunization and mock- immunization groups

Participant type(s)

Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
55 years

Sex
All

Key exclusion criteria
1. Age <18 or >50 (>60 for re-enrollees). Reason for exclusion of children: increased risks associated with the blood volumes needed for this study in individuals undergoing growth or of small body size (<110 POUNDS). Reason for exclusion of older adults: increased risks associated with blood volumes needed for this study in individuals with a greater probability of occult cardiovascular or cerebrovascular disease
2. Pregnant females and females that are breast-feeding. Reason for exclusion: the immunological changes accompanying pregnancy and lactation could alter the results of the assays performed
3. Weight less than 110 lbs. for Groups 1 and 3. Reason: volunteers have to meet NIH donor eligibility criteria of weight > 110 lbs. in order to be apheresed at the NIH facility
4. Known immunodeficiency (e.g. HIV positive), history of autoimmune or connective tissue disease, splenectomy, use of steroids or non-steroidal anti-inflammatory drugs, or any immunosuppressive therapy. Reason for exclusion: immune deficiency or immunosuppressive therapy could affect the immunological responses of volunteers and thus the results of the outcome measurements performed in this study
5. Evidence of active (acute or chronic) hepatitis B or C infection. Reason for exclusion: a serious, underlying medical condition could affect the immunological responses of volunteers (as above) or could increase the risk or severity of adverse events associated with participation in this study.
6. Clinical or laboratory evidence of significant hepatic, renal, cardiac, immunologic or hematologic disease. Reason for exclusion: same as for 5.
7. History of malaria infection, exposure to malaria infection, or receipt of a malaria vaccine. Reason for exclusion: New group 1 volunteers: a principal objective of Stage A is to study the transition from non-immune to immune status, and this will not be possible if volunteers are partially immune prior to immunization; Group 2 volunteers (infectivity controls): any pre-existing immunity could prevent these volunteers from acquiring malaria following challenge, falsely indicating that the challenge sporozoites were not viable; Group 3 volunteers (immunology controls): these are the malaria-negative controls for our laboratory assays, and thus cannot have a history of malaria or exposure to malaria. NB1: This criterion does not apply to the six volunteers from the previous irradiated sporozoite protocol who may elect to enroll in this protocol. NB2: If it is impossible to find enough volunteers meeting this criterion, it may be relaxed for Groups 1 and 3 (e.g., volunteers will not be excluded because of history of exposure to malaria)
8. History of anaphylactic reaction to mosquito bites for Groups 1 and 2 volunteers, or Group 3

volunteers if they are to undergo mock-immunization. Reason for exclusion: to avoid increased risk of anaphylaxis
9. Any other significant finding which in the opinion of the investigator would increase the risk of an adverse outcome for volunteers in this protocol, or to compromise the scientific objectives of this protocol

Date of first enrolment
01/09/1999

Date of final enrolment
01/08/2002

Locations

Countries of recruitment
United States of America

Study participating centre
Naval Medical Research Center
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Sponsor information

Organisation
US Army Medical Research and Materiel Command

ROR
https://ror.org/03cd02q50

Funder(s)

Funder type
Government

Funder Name
United States Military Infectious Diseases Research Program

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	22/07/2016		Yes	No