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A study to investigate the dose of Bilharzia worms that can be safely used to infect humans as a first step to enable testing Bilharzia vaccines

Submission date
12/01/2021

Registration date
01/02/2021

Last Edited
18/12/2025

Recruitment status
Recruiting

Overall study status
Ongoing

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
Schistosomiasis (also known as bilharzia) is a disease of global importance, with an estimated 240 million people worldwide affected. It is caused by worms called schistosomes. In Uganda, about 30% of the population is infected and 50% of the population is at risk. The disease is caused mainly when the male and female worms pair up in the human body and the eggs produced by the female worm are deposited. The body's immune system reacts to the eggs leading to scarring within the organs where the eggs are located. This eventually results in disease in the liver, spleen, intestines, bladder and kidneys. Individuals with schistosomiasis may develop abdominal distension, vomit blood and pass blood in stool or urine.
Currently, there is no vaccine against schistosomiasis. As part of the traditional vaccine development process, vaccine candidates must be tested for their benefit in large-scale field studies. Usually, for such studies, the endpoint is the occurrence of infection or disease following natural exposure. Such studies require a long duration and/or large population sizes to obtain a good estimate of how well the vaccine works. Conducting controlled, experimental infection studies has been shown to eliminate several disadvantages of this traditional approach. Researchers at the Leiden University Medical Centre in the Netherlands have developed a controlled human infection model for schistosomiasis in Dutch volunteers and found it to be feasible and safe. Schistosomiasis is non-existent in the Netherlands but in settings such as Uganda where schistosomiasis is common, the response to this controlled infection and to candidate vaccines is expected to be different. This study aims to implement in Uganda the controlled infection model conducted in the Netherlands, so that it can be used for testing the safety of candidate schistosomiasis vaccines and how well they work in a setting where the infection is common.
The study will investigate whether infection with young male schistosomes (called cercariae) is safe and tolerable. It will also investigate the doses at which the male cercariae can establish infection in healthy adult Ugandan volunteers. Male worms do not produce eggs. This infection with male cercariae will be done among volunteers with minimal prior exposure to schistosomiasis and those with intense prior exposure to schistosomiasis. The study will also

investigate how the infection establishes itself in the body and the effect of the infection on the body's immune system. The study will also investigate volunteer and wider community understandings of the controlled human infection model of schistosomiasis in Uganda.

Who can participate?
Healthy human volunteers aged 18-45 from the two study settings (one with minimal prior schistosome exposure, one with intense prior exposure)

What does the study involve?
In each setting, groups of 3 or 7 volunteers will be exposed to doses of between 10 and 30 cercariae. The cercariae will be taken from a laboratory strain of schistosome originally isolated in Puerto Rico. Depending on the outcome of low-dose infection, the dose will be increased or additional volunteers will be exposed to the same number of cercariae. Volunteers will have their skin exposed to single-sex cercariae once.
The main study endpoints are the frequency and magnitude of adverse events after controlled human infection and the number of male cercariae at which 100% of volunteers show detectable infection. Infection will be tested using the highly sensitive circulating anodic antigen (CAA) test for schistosomiasis. The other endpoints are the time to positive serum CAA test, and immune responses directed against schistosomes.
Volunteers will be intensively followed up for 24 weeks, with a further follow-up time point at 52 weeks. Volunteers will be requested to visit the clinical trial centre weekly after infection for 12 weeks to record adverse events. After this, two-weekly visits will continue until week 24. A final follow-up visit will be after 1 year. Blood and urine samples will be taken at every visit. Volunteers will keep a diary to register adverse events up to 24 weeks.
Immediately CAA is detected (expected around 6 to 8 weeks after infection) participants will be treated with praziquantel to cure the schistosomiasis infection. Praziquantel may be repeated 4 weeks later if CAA levels do not fall to zero. Volunteers will be required to avoid contact with potentially schistosome-contaminated water until the controlled infection has been shown to have been effectively cured, potentially a period of up to 14 weeks.

What are the possible benefits and risks of participating?
There is no direct benefit for participants. The risks are those related to infection with male schistosomes. A rash called Swimmer's Itch may occur at the point of entry of the worms. Only mild forms of the itch are expected to occur because a small number of worms will be used. Fever, fatigue, body aches, malaise and non-productive cough (as a result of Katayama fever) may also occur. The chances of developing Katayama fever are very low in Uganda because schistosomiasis is common in Uganda. To minimize the risk of volunteers acquiring a natural infection concurrently with the controlled infection, there will be careful education and selection of volunteers and early treatment of infection. The volunteers will incur a loss of income, as well as transport costs and clinic visit time. These will be considered in the planned remuneration.

Where is the study run from?
The study is run from the MRC/UVRI and LSHTM Uganda Research Unit in Entebbe (Uganda)

When is the study starting and how long is it expected to run for?
November 2017 to May 2027

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Professor Alison Elliott, alison.elliott@lshtm.ac.uk/alison.elliott@mrcuganda.org

Contact information

Type(s)
Scientific

Contact name
Prof Alison Elliott

ORCID ID
https://orcid.org/0000-0003-2818-9549

Contact details
MRC/UVRI and LSHTM Uganda Research Unit
Plot 51-59, Nakiwogo Road
PO Box 49
Entebbe
Uganda
-
+256 (0) 417704000 / +256 (0)312262911
Alison.Elliott@lshtm.ac.uk

Type(s)
Public

Contact name
Prof Alison Elliott

Contact details
MRC/UVRI and LSHTM Uganda Research Unit
Plot 51-59, Nakiwogo Road
PO Box 49
Entebbe
Uganda
-
+256 (0) 417704000 / +256 (0)312262911
alison.elliott@mrcuganda.org

Type(s)
Scientific

Contact name
Dr Ronald Kiyemba

ORCID ID
https://orcid.org/0000-0002-2094-4573

Contact details
MRC/UVRI and LSHTM Uganda Research Unit, PO Box 49
Entebbe
Uganda
-
+256 (0)702311161
Ronald.Kiyemba@mrcuganda.org

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Wellcome Trust grant number 218454/Z/19/Z

Study information

Scientific Title
Establishing a single-sex controlled human Schistosoma mansoni infection model for Uganda: safety and dose finding

Acronym
CHI-S-Ug1

Study objectives
Primary objective:
1. To investigate the safety, tolerability and infectivity of male Schistosoma mansoni cercariae in (1) healthy adult Ugandan volunteers with minimal prior exposure to Schistosoma mansoni, and (2) healthy adult Uganda volunteers with intense prior exposure to Schistosoma mansoni

Exploratory objectives:
1. To investigate the kinetics of controlled infection with male Schistosoma mansoni cercariae in (1) healthy adult Ugandan volunteers with minimal prior exposure to Schistosoma mansoni, and (2) healthy adult Ugandan volunteers with intense prior exposure to Schistosoma mansoni.
2. To investigate immunological, metabolic and microbiome changes after infection with Schistosoma mansoni male cercariae.
3. To investigate volunteer and wider community understandings of CHI in the context of CHI-S, specifically to (1) assess volunteers' and wider community responses to CHI-S in Uganda, and (2) compare experience between pathogens and countries.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 06/04/2020, Uganda Virus Research Institute Research Ethics Committee (Plot 51-59 Nakiwogo Road, Entebbe; PO Box 49 Entebbe, Uganda; +256 (0)414320631; REC@uvri.go.ug),

ref: GC/137/20/04/773
2. Approved 17/11/2020, Uganda National Council for Science and Technology (Plot 6 Kimera Road, Kampala; P. O. Box 6884 Kampala, Uganda; +256 (0)414705500; info@uncst.go.ug), ref: HS697ES
3. Approval pending, London School of Hygiene and Tropical Medicine Observational / Interventions Research Ethics Committee (Keppel Street, London, WC1E 7HT, UK; +44 (0) 2076368636; ethics@lshtm.ac.uk)

Study design
Single-centre open-label dose-escalation trial

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Schistosomiasis

Interventions
Healthy human volunteers will be enrolled from two settings; one with minimal prior schistosome exposure and another with intense prior exposure, both in Uganda. In each setting, groups of volunteers will be dermally exposed to single-sex (male) cercariae once at doses of between 10 and 30 cercariae. Depending on the outcome of the low dose infection, the dose will be escalated or additional volunteers will be exposed to the same number of cercariae. Volunteers will undergo intensive follow-up for 24 weeks and a late follow-up time point at 52 weeks. They will visit the clinical trial centre weekly after infection for 12 weeks. After this, two-weekly visits will continue until week 24. A final follow up visit will be after one year. During the visits, adverse events will be recorded, levels of Schistosoma mansoni circulating anodic antigen (CAA) will be measured and samples obtained for immunological analyses. Immediately CAA is detected (expected around 6 to 8 weeks after infection) the volunteers will be treated with praziquantel to cure the Schistosoma infection. Praziquantel may be repeated 4 weeks later if CAA levels do not fall to zero. Volunteers will be required to avoid contact with potentially Schistosoma mansoni-contaminated water until the controlled infection has been shown to have been effectively cured, potentially a period of up to 14 weeks. The trial is estimated to last 30 months.

Intervention Type
Other

Primary outcome(s)
1. Frequency and magnitude of adverse events after controlled human Schistosoma mansoni infection with male cercariae measured using a diary kept by the volunteer and a questionnaire filled out at every visit documenting the participants' symptoms and signs. These data will be collected at baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 20, 22, 24 and 52 weeks
2. Number of male cercariae at which 100% of volunteers show patent infection, i.e. detectable Schistosoma mansoni circulating anodic antigen (CAA), measured using the predefined dose of cercariae administered and a serum CAA assay. A patent infection will be defined as a positive serum CAA test (>1.0 pg/ml) at any time between 0 and 12 weeks following infection with cercariae. CAA will be measured at baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks

Key secondary outcome(s))
1. Time to positive serum and urine CAA (Circulating Anodic Antigen) test measured using a serum and urine CAA assay after infection at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks
2. Comparison of the height of the peak serum CAA concentration in different dose groups measured using a serum CAA assay at baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 weeks
3. Humoral (antibody) responses directed against Schistosoma mansoni antigens measured using antibody assays by immunofluorescence and/or enzyme-linked immunosorbent assays (ELISAs) and/or antibody arrays for specific Schistosoma mansoni proteins or glycans at baseline, 4, 8, 12, 14, 16, 18, 20, 22, 24 and 52 weeks
4. Cellular responses directed against Schistosoma mansoni antigens measured using multi-parameter flow cytometry, mass cytometry time-of-flight (CyToF) and enzyme-linked Immune absorbent spot (ELISPOT) assays with or without using Schistosoma mansoni-specific in vitro stimulation at baseline, 4, 8, 12, 14, 16, 18, 20, 22, 24 and 52 weeks
5. Metabolic changes before and after controlled human Schistosoma mansoni infection with male Schistosoma mansoni cercariae measured by metabolic profiling of serum and urine samples at baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24 and 52 weeks
6. Changes in microbiome after controlled human Schistosoma mansoni infection with male Schistosoma mansoni cercariae measured using bioinformatic sequencing pipelines at baseline, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 20, 22, 24 and 52 weeks

Completion date
31/05/2027

Eligibility

Key inclusion criteria
1. Volunteer is aged ≥18 and ≤45 years and in good health
2. Volunteer is able to communicate well with the research team members and is available to attend all study visits
3. Volunteer has an adequate understanding of the procedures of the study and agrees to abide strictly thereby
4. Volunteer will remain within Uganda during the study period and is reachable by mobile telephone from until at least week 16 of the study period
5. Volunteer understands the need to avoid contact with waterbodies where Schistosoma is transmitted and can demonstrate that they are able and willing to do so for the full 12-16 week period until the controlled infection has been cured
6. Volunteer agrees to refrain from blood donation throughout the study period
7. For a female volunteer: volunteer agrees to use adequate contraception and not to breastfeed for the duration of the study
8. Volunteer has signed informed consent

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
45 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Evidence of current Schistosoma infection based on highly sensitive CAA assay (at a conservative cut-off level of >0.5 pg/ml)
2. Evidence of malaria or of intestinal helminth infections (if identified, these will be treated and the volunteer may be reconsidered for inclusion)
3. 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, immune-deficient, psychiatric and other disorders, which could compromise the health of the volunteer during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following. Note that volunteers may be reconsidered for inclusion following recovery from treatable conditions:
3.1. Temperature ≥37.5°C/99.5°F
3.2. Body weight <50 kg or Body Mass Index (BMI) <18.0 or >30.0 kg/m² at screening
3.3. Positive HIV, HBV or HCV screening tests
3.4. The use of immune modifying drugs within three months prior to study onset (inhaled and topical corticosteroids and oral anti-histamines exempted) or expected use of such during the study period
3.5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years
3.6. Any history of treatment for severe psychiatric disease by a psychiatrist in the past year
3.7. History of drug or alcohol abuse interfering with normal social function in the period of 1 year prior to study onset
3.8. Any clinically significant abnormalities (including extended QT interval) on electrocardiogram
4. The chronic use of any drug known to interact with praziquantel, artesunate or lumefantrine metabolism (e.g. phenytoïn, carbamazepine, phenobarbital, primidone, dexamethasone, rifampicin, cimetidine, flecainide, metoprolol, imipramine, amitriptyline, clomipramine, class IA and III antiarrhythmics, antipsychotics, antidepressants, macrolides, fluoroquinolones, imidazole- and triazole antimycotics, antihistamines). Because lumefantrine may cause extension of QT-time, chronic use of drugs with effect on QT interval are excluded from the study
5. For female volunteers: positive urine pregnancy test at screening, or breastfeeding
6. Known hypersensitivity to or contra-indications (including co-medication) for use of praziquantel, artesunate or lumefantrine
7. Participation in another research study involving receipt of an investigational product in the 30 days preceding enrolment, or planned use during the study period
8. Being an employee or student of the Uganda Virus Research Institute or its campus partners, or of Entebbe Hospital

9. Volunteer who, in the opinion of the investigator, does not fully understand the purpose of the study or requirements for participation or is unlikely to adhere to the requirements of the study

Date of first enrolment
31/12/2025

Date of final enrolment
28/02/2027

Locations

Countries of recruitment
Uganda

Study participating centre
MRC/UVRI and LSHTM Uganda Research Unit
Immunomodulation and Vaccines programme
Plot 51-59 Nakiwogo Road
Entebbe
Uganda
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Sponsor information

Organisation
London School of Hygiene & Tropical Medicine

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Upon completion of data entry and cleaning, clinical and laboratory data will be anonymised and deposited in LSHTM data compass and a weblink generated. Data will be made available upon reasonable request after the publication of the trial results.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		20/07/2023	04/08/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes