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Investigation of genetic markers for drug resistance in Schistosoma haematobium parasites in Pemba

Submission date
02/09/2024

Recruitment status
No longer recruiting

Registration date
24/10/2024

Overall study status
Ongoing

Last Edited
15/09/2025

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
Zanzibar has an impressive track record implementing mass drug administration (MDA) with praziquantel (PZQ) against Schistosoma haematobium infections since the 2000s, achieving elimination of schistosomiasis as a public health problem in most areas, with a possibility of interruption of transmission. However, a few hotspots with a high prevalence of infection (5-10%) remain. This project is set in Pemba (Zanzibar, Tanzania), where it is thought that the MDA-driven selection of drug-resistant parasite strains is contributing to persistent transmission in hotspots. Recent revolutionary advances in understanding the molecular basis of PZQ action mean that for the first time we are able to screen natural Schistosoma populations for genetic signatures that may point to reduced PZQ effectiveness or even resistance. With a combination of parasitological fieldwork, genomic analyses and mathematical modelling this project aims to deliver new insights into how in Pemba, MDA has shaped the genetic diversity of S. haematobium populations over space and time, how this may be affecting drug effectiveness contributing to persistent hotspots and lastly how emerging resistance can best be monitored and mitigated. Thus, this study will lay the foundations for population-based research into drug resistance in Schistosoma species having important implications for novel drugs in the pipeline. The main aim is to genetically profile S. haematobium miracidia from different locations in Pemba and identify any genetic markers associated with PZQ resistance.

Who can participate?
The study will be implemented on Pemba island for 1 year in 2024/25. Cross-sectional surveys will be conducted in 15 schools and a longitudinal survey will be conducted in two schools in Pemba. Schoolchildren, male and female, aged 5-16 years from nursery till grade 7 will be invited to participate in the school-based surveys.

What does the study involve?
Participants from all 17 schools will be invited to answer a questionnaire about their demographics and past anti-schistosomal treatments. Participants from the 15 schools where the cross-sectional surveys take place will be tested for S. haematobium infection based on a single examination of a single urine sample with the urine filtration method. Participants from

the two schools where a longitudinal survey is conducted will be invited to submit five urine samples on consecutive days before a mass drug administration (MDA) of praziquantel conducted by the Zanzibar Neglected Tropical Diseases (NTD) Program takes place. During the MDA, it will be recorded who takes praziquantel and how many tablets. Two weeks after the MDA, the participants will be asked again to submit five urine samples on consecutive days. The miracidia (parasite larvae) will be hatched from the S. haematobium eggs contained in the urine samples from infected individuals. The genetic profile of the miracidia will be analysed (i) to quantify spatiotemporal patterns in the genetic diversity of S. haematobium; and (ii) before and 2 weeks after praziquantel MDA to determine the potential selection of genetic variants and any association between genetic variants and praziquantel sensitivity. In statistical analyses, the observed individual and population-level S. haematobium egg reduction rates will be correlated with genetic signatures and the underlying worm-level PZQ effectiveness will be estimated to inform modelling. Using mathematical modelling, the impact of MDA with PZQ and mitigation strategies on population dynamics of drug resistance in S. haematobium will be predicted. Cost-efficient survey strategies for pharmacovigilance will be designed.

What are the possible benefits and risks of participating?
The direct benefit of participation in the study is that participants will be informed about their S. haematobium infection status and will receive treatment with praziquantel. The treatment can improve the general health status of children, including less pain, fatigue and weakness and thus improved school or working performance.
For the participants, no risks are involved in producing a fresh urine sample. Discomfort might be created by the transparency of the urine containers handed out for submission, but it will be pointed out to participants that they can submit the container wrapped in a paper or cloth if they prefer to avoid others seeing the colour of their urine.
The questionnaires will include some questions that might be embarrassing, discomforting or too personal; however, participants can deny responding to these questions when they decide to participate.
The indirect benefit is that this project will enable a better understanding of the effectiveness of current schistosomiasis control and elimination strategies in Pemba, which can be adapted in line with our findings. Hence, there is a positive impact (immediate and long-term) on the health of the human population of Pemba.

Where is the study run from?
1. Public Health Laboratory-Ivo de Carneri, Pemba (Tanzania)
2. Erasmus MC, Rotterdam (Netherlands)
3. Swiss Tropical and Public Health Institute, Allschwil (Switzerland)
4. Natural History Museum, London (UK)

When is the study starting and how long is it expected to run for?
March 2023 to August 2027

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
1. Dr Luc Coffeng (l.coffeng@erasmusmc.nl)
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Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
312326/Z/24/Z

Study information

Scientific Title
Resistance Evaluation and Surveillance Initiative for Schistosomiasis Treatment

Acronym
RESIST

Study objectives
Study hypothesis: mass drug administration (MDA)-driven selection of praziquantel drug-resistant Schistosoma haematobium strains is contributing to persistent transmission in hotspots.

The primary study objective is to assess the genetic profile of S. haematobium miracidia from different locations in Pemba and identify potential genomic praziquantel resistance markers. The researchers will assess population structuring across the genome using the fixation index (FST) calculated regionally across the genome for pairwise comparisons of populations partitioned by location (e.g., school). We will do this using a Bayesian framework (so no hypothesis testing), using software like BayeScan v2.1.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 13/08/2024, Ethikkommission Nordwest und Zentralschweiz (Hebelstrasse 53, Basel, 4056, Switzerland; +41 (0)61 268 13 50; eknz@bs.ch), ref: AO-2024-00084

2. approved 24/09/2024, Zanzibar Health Research Ethics Committee (Binungini, P.O. Box 236, Unguja, Not applicable, Tanzania; +255 (0)776 264 880; zahrec@zahri.go.tz), ref: ZAHREC/01/PR/Sept/2024/33

Study design
Investigator-initiated single-centre observational research study

Primary study design
Observational

Study type(s)
Other, Efficacy

Health condition(s) or problem(s) studied
Schistosoma haematobium

Interventions
The study is designed as an observational study with the following components:
1. Cross-sectional surveys: Collect single urine samples from students in 15 schools that were also part of the Zanzibar Elimination of Schistosomiasis Transmission (ZEST) study to assess the

geographic distribution of S. haematobium prevalence and intensity of infection, and for miracidia isolation from viable S. haematobium eggs of infected individuals.
2. Longitudinal surveys: Collect quintuple urine samples from students in two schools before and 2 weeks after praziquantel MDA to assess S. haematobium egg reduction rates (ERR), estimate praziquantel drug efficacy and effectiveness of MDA, and for miracidia isolation from viable S. haematobium eggs of infected individuals
3. Perform genomic analyses of isolated and preserved S. haematobium miracidia, collected:
3.1. From across Pemba over multiple time points (2012 and 2017 from the SCAN archives, and 2024/25 from this study) to quantify spatiotemporal patterns in genetic diversity of S. haematobium
3.2. Before and 2 weeks after praziquantel MDA to determine the potential selection of genetic variants and any association between genetic variants and praziquantel sensitivity
4. Correlate observed individual and population-level S. haematobium ERR with genetic signatures and estimate underlying worm-level praziquantel efficacy to inform modelling
5. Predict the impact of MDA with praziquantel and mitigation strategies on population dynamics of drug resistance in S. haematobium, using the data from objectives 1 and 2
6. Design cost-efficient survey strategies for pharmacovigilance.

Hence, with a combination of parasitological fieldwork, genomic analyses, and mathematical modelling, this project will deliver new insights into how MDA has shaped the genetic diversity of S. haematobium over space and time in Pemba, how this has potentially affected drug efficacy and contributed to the persistence of hotspots, and how emerging resistance can best be monitored and mitigated.

Of note, the MDA that takes place during the study period is implemented irrespective of the RESIST study by the Neglected Tropical Diseases (NTD) Programme of the Zanzibar Ministry of Health.

Intervention Type
Other

Primary outcome(s)
Frequency of praziquantel resistance associated single nucleotide polymorphisms (SNPs) in S. haematobium miracidia collected in the school surveys in 2024/25 as measured using whole genome sequencing (WGS) methodologies and bioinformatic pipelines/tools.

Key secondary outcome(s))
1. Genome assemblies and TRPMPZQ SNP profiles of S. haematobium miracidia from 17 different schools in Pemba, collected in 2024/25, as measured using WGS methodologies and bioinformatic pipelines/tools
2. Genome assemblies and TRPMPZQ SNP profiles of S. haematobium miracidia from the same 17 schools in Pemba, collected as part of the ZEST study in 2012 and 2017, and archived in SCAN, as measured using WGS methodologies and bioinformatic pipelines/tools
3. Genome assemblies and TRPMPZQ SNP profiles of S. haematobium miracidia collected before and after MDA from two different schools in Pemba in 2024/25, as measured using WGS methodologies and bioinformatic pipelines/tools
4. Spatiotemporal genetic diversity patterns of S. haematobium populations across Pemba in 2012, 2017 and 2024/25, as measured by the fixation index (FST)
5. Associations between genetic variants and PZQ sensitivity measured by ERR in two different schools in Pemba in 2024/25, based on pairwise comparisons of parasite sub-populations in terms of the FST, partitioned by the individual-level egg reduction rates

6. Associations between genetic variants and PZQ sensitivity in terms of Ca2+ influx in HEK293 cells, measured by functional profiling of TRPMPZQ SNPs in two different schools in Pemba in 2024/25
7. Prevalence and intensity of S. haematobium infections in schoolchildren from 17 schools in 2024/25, as measured by urine filtration
8. Prevalence and intensity of S. haematobium infections in schoolchildren from two schools before and after MDA in 2024/25, as measured by urine filtration
9. Individual and population-level S. haematobium ERR of MDA in two different locations in Pemba in 2024/25, based on the population-level arithmetic mean egg counts before and after treatment
10. Model-predicted impact of praziquantel MDA and praziquantel resistance mitigation strategies on trends in S. haematobium infection prevalence and intensity and drug efficacy (ERR)
11. Cost-efficient survey strategies for pharmacovigilance, based on the trade-off of survey cost versus the conditional probability of detecting the presence of reduced drug efficacy due to resistance

Completion date
31/08/2027

Eligibility

Key inclusion criteria
The study population will consist of children attending 17 schools in Pemba, Tanzania:
1. Attendance of grades 1-7 in one among the 17 schools selected to be part of the study
2. Aged 5-16 years
3. Randomised to participate in the study (if the number of attending children is greater than required)
4. Written informed consent signed by the parents
5. Written assent signed by the participant if aged 12-16 years old

Participant type(s)
Learner/student

Healthy volunteers allowed
No

Age group
Child

Lower age limit
5 years

Upper age limit
16 years

Sex
All

Total final enrolment

14155

Key exclusion criteria
1. Not attending any of the 17 selected schools
2. Not attending grades 1-7
3. Not aged 5-16 years
4. Not randomised to participate in the study (if the number of attending children is greater than required)
5. No written informed consent signed by the parents submitted
6. No written assent signed by the participant if aged 12-16 years old
7. Clinically significant severe disease

Date of first enrolment
01/11/2024

Date of final enrolment
17/07/2025

Locations

Countries of recruitment
Tanzania

Study participating centre
Public Health Laboratory-Ivo de Carneri
PO Box 122, Wawi
Pemba
Tanzania
Not applicable

Sponsor information

Organisation
Swiss Tropical and Public Health Institute

ROR
https://ror.org/03adhka07

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository.
After conclusion of the project, the anonymised parasitological data will be curated and disseminated via the Infectious Diseases Data Observatory (https://www.iddo.org/).
All S. haematobium genetic data will be made available via the open access WormBase platform ParaSite (https://parasite.wormbase.org/index.html). Additionally, ShTRPMPZQ variant profiles will be catalogued within TRP Tracker (https://www.trptracker.live/) to enable open access viewing of the functional effect of variants.
All model source codes, documentation, and codes to perform analyses for this project will be version-controlled and made publicly available via GitLab (https://gitlab.com/), and model-simulated data will be made available via Zenodo (https://zenodo.org/).

IPD sharing plan summary
Stored in publicly available repository, Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		08/01/2026	14/01/2026	Yes	No