Study Title: SEROLOGICAL TESTING AND TREATMENT FOR PLASMODIUM VIVAX MALARIA: A CLUSTER-RANDOMIZED TRIAL IN ETHIOPIA

Short title: PvSTATEM

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Phase of the trial: IV

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Study background and Rationale

The resilience of *P. vivax* to malaria elimination efforts is due to its ability to form dormant liver stages (hypnozoites) that reactivate weeks to months after the initial infection causing recurrent episodes of malaria (relapses) and ongoing parasite transmission. Relapses account for 60-90% of recurrent infections and clinical cases of *P. vivax* malaria, and therefore have a significant effect on morbidity at the individual level.

A serological test based on selected *P. vivax* antigens can detect recent exposure and predict future relapses. By coupling this test with a safe and efficacious primaquine treatment regimen, we can create a population-based intervention to target the hypnozoite reservoir. We denote this intervention *P. vivax* Serological Testing and Treatment (PvSeroTAT). The study will provide insights into the feasibility, acceptability, and efficacy of the PvSeroTAT approach. This study will provide insights into the feasibility, acceptability, and efficacy of the PvSeroTAT approach. In this study, individuals, randomized by clusters, will be tested for the presence of serological markers of a recent *P. vivax* infection, followed by a targeted drug treatment intervention aimed at killing P. vivax hypnozoites.

Objective

To compare the effect of community-wide PvSeroTAT with primaquine versus standard clinical practice on mean cluster prevalence of PCR detectable Plasmodium vivax blood-stage infections 6 months after the second round of PvSeroTAT.

Primary endpoint

- PCR detectable P. vivax blood-stage infections 6 months after the second round of PvSeroTAT.
- PCR-detectable P. vivax infections at 6, 12, and 18 months post-PvSeroTAT compared to baseline
- Incidence of clinical P. vivax and P. falciparum malaria at 6, 12, and 18 months
- Hb levels and change from baseline at days 0, 2, 6, and 12
- Incidence of clinically relevant haemolysis (Hb drop ≥25%)

Primary Objectives and Outcome Measures

To compare the effect of community-wide PvSeroTAT with primaquine versus standard clinical practice on mean cluster prevalence of PCR detectable *Plasmodium vivax* blood-stage infections.

Outcome Measures:

- PCR detectable P. vivax blood-stage infections 6 months after the second round of PvSeroTAT.

Secondary Objectives and Outcome Measures

- To assess intervention impact on P. vivax prevalence at 6, 12, and 18 months
- To compare incidence of clinical P. vivax and P. falciparum malaria at health facilities.
- To evaluate safety signals related to primaquine (e.g., haemolysis, low Hb).
- To quantify diagnostic coverage, treatment initiation, and adherence.
- To evaluate the acceptability and cost-effectiveness of the intervention.
- To characterize population-level prevalence of genetic and immunological markers
- To monitor antimalarial resistance markers and pfhrp2/3 deletions.
- To assess the transmission potential of incident and recurrent infections.
- To evaluate household-level mosquito exposure linked to infection recurrence.
- To quantify antibody responses to *P. vivax* and a panel of public health relevant pathogens.

Outcome Measures

- PCR detectable P. vivax blood-stage infections 12 months after the second round of PvSeroTAT
- PCR detectable P. vivax blood-stage infections 6 months after the first round of PvSeroTAT
- PCR-detectable P. vivax infections at 6, 12, and 18 months post-PvSeroTAT compared to baseline
- Incidence of clinical P. vivax and P. falciparum malaria at 6, 12, and 18 months
- Hb levels and change from baseline at days 0, 2, 6, and 12
- Incidence of clinically relevant haemolysis
- Serious adverse events (SAEs): number, severity, outcomes, and relatedness to intervention
- Coverage of serological testing and proportion refusing participation or treatment
- Primaquine treatment uptake and adherence
- Prevalence of antibodies to other major infectious diseases
- Prevalence of G6PD deficiency, hemoglobinopathies, Cyp2D6 polymorphisms, and Duffy phenotypes
- Prevalence of antimalarial resistance markers and pfhrp2/3 gene deletions
- Prevalence of PfHRP2 and PvLDH antigens
- Cost per averted symptomatic P. vivax case
- Frequency of P.vivax recurrences after hypnozoite clearance
- Contribution of incident vs recurrent P. vivax infections to mosquito transmission
- Mosquito exposure patterns for incident vs recurrent infections

Study Design

This study is a two-arm, cluster-randomized, open-label, controlled intervention trial conducted over two years.

Study population

The target population consists of all the residents of Shashemene zuriya, Arsi Negele or Shalla woredas located in the Oromia Region of Ethiopia.

Eligibility Criteria

Inclusion Criteria:

- Participants will remain in the study area for the next 30 days.
- The participant is older than 12 months.

Exclusion criteria:

- Known allergy or history of adverse reaction or chronic/congenital disease in which any of the contraindicated intervention drugs are contraindicated: Primaquine and chloroquine.
- Individuals with severe malnutrition or signs of severe disease
- Inability to tolerate oral treatment
- The participant is unwilling to participate.
- Individuals with G6PD level ≤ 4 U/ g Hb Pregnant women, women unwilling to undergo a pregnancy test to confirm non-pregnancy status, and breastfeeding mothers with infants younger than 6 months or whose infants have not been confirmed to be G6PD normal.
- All lactating women
- Hb level <8gram per deciliter.
- Previous episode of haemolysis or severe haemoglobinuria following primaquine.
- Use of other medication associated with haemolysis, which will be detailed in an SOP.
- Useofothermedicationsknowntointerferewiththepharmacokineticsofprimaquine, which will be detailed in an SOP.
- Blood transfusion in the last 90 days, as this can falsely elevate G6PD activity in deficient participants.

Study duration

24 months

Investigational Medicinal Product

-Chloroquine 250mg

-Primaquine 15mg

Study Arms

Arm: 1= (PvSeroTAT intervention)

Arm: 2 = (Control arm)

Sample size

9600 individuals (24 clusters, 400 individuals per cluster) will be included in this cluster randomized trial. 12 clusters (4800 individuals) will be randomized to the PvSeroTAT intervention arm, 12 clusters (4800 individuals) will be randomized to the control arm.

Evaluator's Risk/Benefit Assessment:

Based on the available data, the current trial (PvSTATEM) is sufficient to support the proposed clinical trial. The trial is justified and aligns with Good Clinical Practice. The potential benefits are believed to outweigh the risks, assuming the study follows the approved protocol, relevant local regulations, ethical standards and the principles of Good Clinical Practice.