FocaL mass drug Administration for vivax Malaria Elimination (FLAME)

Kick-off meeting, ASTMH 2022

Michelle Hsiang and Alejandro Llanos-Cuestas
November 2, 2022
Universidad Cayetano Peruana Heredia (UPCH) Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
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<tbody>
<tr>
<td>Alejandro Llanos-Cuestas, Site-PI</td>
<td>Oversight, study design, trial implementation</td>
</tr>
<tr>
<td>Gabriel Carrasco, Co-Investigator</td>
<td>Spatial analyses, serology, oversee data management</td>
</tr>
<tr>
<td>Angel Rosas-Aguirre, Co-Investigator</td>
<td>Economic analysis</td>
</tr>
<tr>
<td>Hugo Rodriguez, Collaborator</td>
<td>Engagement/training with village health promoters, field staff</td>
</tr>
<tr>
<td>Veronica Soto Calle, Project Manager</td>
<td>Project management</td>
</tr>
<tr>
<td>Astrid Altamirano Quiroz, Field Coordinator, Medical Officer</td>
<td>Field coordination, Safety monitoring and adverse event management</td>
</tr>
<tr>
<td>Paulo Manrique Valverde, Lab Coordinator</td>
<td>Lab operations, supply procurement</td>
</tr>
<tr>
<td>Diamantina Moreno-Gutierrez, Senior Research Analyst</td>
<td>Economic analysis</td>
</tr>
<tr>
<td>Brenda Soraya Urdar Ruiz, Pharmacist</td>
<td>Drug storage, distribution, regulatory oversight</td>
</tr>
<tr>
<td>TBD, Data Manager</td>
<td>Data management</td>
</tr>
<tr>
<td>TBD, Internal Monitor</td>
<td>Conducting and maintaining QA/QC internal monitoring reports</td>
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# UCSF Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
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<tbody>
<tr>
<td>Michelle Hsiang, PI</td>
<td>Oversight, study design, coordinate input from investigators</td>
</tr>
<tr>
<td>Bryan Greenhouse, Co-Investigator</td>
<td>Support molecular and serological studies including genomic surveillance</td>
</tr>
<tr>
<td>Sydney Fine, Research Coordinator</td>
<td>Project coordination, SOP, data collection oversight</td>
</tr>
<tr>
<td>Michelle Roh, Post-doctoral fellow</td>
<td>Support interim analyses and conduct sub-studies on operational aspects of fMDA (timing, coverage)</td>
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<tr>
<td>Xue Wu, Data Analyst</td>
<td>Support data analysis</td>
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</tbody>
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## Additional Collaborators

<table>
<thead>
<tr>
<th>Institution</th>
<th>Name</th>
<th>Role</th>
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<tbody>
<tr>
<td>PATH</td>
<td>Adam Bennett, Co-I</td>
<td>CRCT design and analysis, geospatial analyses</td>
</tr>
<tr>
<td></td>
<td>Gonzalo Domingo, Collaborator</td>
<td>G6PD testing</td>
</tr>
<tr>
<td>Stanford</td>
<td>Jade Benjamin Chung, Co-I</td>
<td>Trial biostatistician, spillover analyses</td>
</tr>
<tr>
<td>EOCRU</td>
<td>Kevin Baird, Collaborator</td>
<td><em>P. vivax</em> treatment, G6PD deficiency, safety, CYP2D6</td>
</tr>
<tr>
<td>Menzies</td>
<td>Sarah Auburn, Collaborator</td>
<td><em>P. vivax</em> genomics</td>
</tr>
<tr>
<td></td>
<td>Ric Price, Collaborator</td>
<td><em>P. vivax</em> treatment, G6PD deficiency, safety, <em>P. vivax</em> genomic surveillances, economic analyses</td>
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</tbody>
</table>
Plan Malaria Cero

Norma Legal Nacional – Aprobación del Plan Malaria Cero 12 Abril 2017

12 NORMAS LEGALES Miércoles 12 de abril de 2017 / El Peruano

Aprueban el Documento Técnico: “Plan Malaria Cero Periodo 2017-2021”

RESOLUCIÓN MINISTERIAL N° 244-2017/MINSA

Lima, 11 de abril del 2017


CONSIDERANDO:

Que, los numerales I y II del Título Preliminar de la Ley N° 26842, Ley General de Salud, señalan que la salud es condición indispensable del desarrollo humano y medio fundamental para alcanzar el bienestar individual y colectivo. La protección de la salud es de interés público. Por tanto, es responsabilidad del Estado regularla, vigilarla y promoverla;

en la región Amazónica con enfoque comunitario e intercultural con una primera etapa entre los años 2017 al 2021;

Estando a lo propuesto por la Dirección General de Intervenciones Estratégicas en Salud Pública;

Que, mediante el Informe N° 254-2017-OGAJ/MINSA, la Oficina General de Asesoría Jurídica ha emitido opinión legal;

Con el visado de la Directora General de la Dirección General de Intervenciones Estratégicas en Salud Pública, del Director General de la Oficina General de Asesoría Jurídica, de la Viceministra de Salud Pública; y

De conformidad con lo dispuesto en el Decreto Legislativo N° 1161, Ley de Organización y Funciones del Ministerio de Salud y el Reglamento de Organización y Funciones del Ministerio de Salud, aprobado por Decreto Supremo N° 007-2018-SA;

SE RESUELVE:

Artículo 1°.- Aprobar el Documento Técnico: “Plan Malaria Cero Periodo 2017-2021”, el mismo que forma parte integrante de la presente Resolución Ministerial.

Artículo 2°.- Encargar a la Dirección General de...
Plan Malaria Cero

<table>
<thead>
<tr>
<th>Stages</th>
<th>Stage I (5 years)</th>
<th>Stage II (15 – 20 years)</th>
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<tbody>
<tr>
<td>Phases</td>
<td>Phase I Control</td>
<td>Phase II Towards the elimination</td>
</tr>
<tr>
<td>Periods</td>
<td>3 years</td>
<td>7 years</td>
</tr>
<tr>
<td>Horizon</td>
<td>3 years</td>
<td>10 years</td>
</tr>
<tr>
<td>Setting</td>
<td>Very high, high, and medium endemicity</td>
<td>Medium and low endemicity</td>
</tr>
<tr>
<td>Main Strategies</td>
<td>- Integral interventions - Pharmacological block</td>
<td>- Pharmacological block. - Detection and treatment for asymptometrically infected - Effectiveness studies</td>
</tr>
<tr>
<td>Impact</td>
<td>↓ 70 %</td>
<td>↓ 90 %</td>
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Elimination of Residual Malaria

UCSF Malaria Elimination Initiative (MEI)
Main Study Objectives

1. Determine the effectiveness of fMDA to reduce *P. vivax* transmission
2. Evaluate the safety and tolerability of fMDA
3. Measure the cost-effectiveness and acceptability of fMDA
Hypotheses

1. fMDA vs control (n=32 villages) will **reduce cumulative** *Pv* **incidence** by ≥55% from mean baseline cluster *Pv* incidence of 161/1000

2. Serious adverse events (SAE) from fMDA will be rare (1/1000), and the incidence of SAE or severe malaria in fMDA will not be higher than the incidence of severe malaria in control arm

3. fMDA is more cost-effective than control and will be acceptable to the community
# Trial Outline

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Open-label cluster randomized control trial</th>
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<tbody>
<tr>
<td>Study period</td>
<td>3 years trial intervention (5 year grant period)</td>
</tr>
<tr>
<td>Study Site</td>
<td>Loreto Department, Peru</td>
</tr>
<tr>
<td>Sample Size</td>
<td>32 clusters or villages (16 per arm), population is ~7600, mean population per cluster ~240</td>
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<tr>
<td>Cluster eligibility</td>
<td>Within 8 hours transport of Iquitos, Incidence: at least 2 cases in year prior to trial and not &gt;500/1000, population size (&lt;1000)</td>
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<tr>
<td>Interventions</td>
<td><strong>Control</strong>: Standard interventions</td>
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<td></td>
<td><strong>fMDA</strong>: Standard interventions PLUS fMDA for high-risk individuals without G6PD deficiency in 2 annual rounds (fMDA regimen includes CQ with TQ for age &gt;=16years, or PQ for age &lt;16)</td>
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# Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th>Aim 1</th>
<th>Aim 2</th>
<th>Aim 3</th>
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| • Cumulative incidence of *Pv* infection  
• *Pv* infection prevalence  
• *Pv* seroprevalence  
• *Pv* genetic diversity  
• As above for *Pf* only, and *Pf/Pv* | • Incidence of SAE  
• Incidence of severe malaria  
• Incidence of any grade 3 AE or higher  
• Tolerability of study drugs | • Cost per *Pv* case averted or DALY, or dollar saved  
• Costs per fMDA round, per capita  
• Refusal rates  
• Willingness to continue to participate (interim and endline surveys) |
Sub-studies

- Human mobility (travel/residence history with genetic data)
- G6PD prevalence
- CYP2D6 epidemiology
- Validation of Pv serological markers of recent exposure
- Optimal timing of fMDA
- Spillover analyses
Study Site: Loreto Department, Peru

- Tropical/subtropical region of the Amazon
- Predominantly Pv
- Perennial transmission, rises between Nov–Jan, peaks in April
- 137 villages in Maynas province (banks of Momon, Nanay, and Pintuyacu Rivers)
  - 4 districts: Alto Nanay, Iquitos, Punchana, and San Juan Bautista
- Prevalence of Pv blood stage infections: 1-25% by highly sensitive PCR
  - >70% are asymptomatic, >70% are also submicroscopic
- Village level incidence: 0-500 API
Cluster selection and randomization

• Determine eligibility among 137 villages in study areas
  • Inclusion criteria: Within 8 hours transport of Iquitos
  • Exclusion criteria:
    • API >500 or <2 cases in year prior to trial
    • Extreme population size (>1000)
    • Agree to participate

• Selection and randomization of 32 villages based:
  • Pv incidence in the prior year
  • distance to Iquitos
  • population density
  • clusters in opposite intervention arms are at least 2 km apart.

• Based on 2019 data, generated 106 valid permutations of 32 clusters. Exercise to be repeated with 2021-2022 data

UCSF Malaria Elimination Initiative (MEI)
Interventions

• **Standard interventions**
  • High coverage of ITNs for vector control
  • Case management (passive)
  • Reactive case detection using microscopy (RACD)

• **fMDA prior to high season by DOT**
  • Rounds 1 - August
    • ≥ 16 years: 3 day CQ (10/10/5 mg/kg) + TQ (300 mg)
    • 6 mos - 16 years: 3 day CQ (10/10/5 mg/kg) + PQ (3.5 mg/kg over 7d)
  • Rounds 2 – October
    • ≥ 16 years: single dose CQ (10 mg/kg) + TQ (300 mg)
    • 6 mos - 16 years: single dose CQ (10 mg/kg) + PQ (3.5 mg/kg over 7d)
  • Will change to pediatric TQ in subsequent rounds if registered during trial
Cluster Randomization

32 clusters (i.e. villages)
total population ~7600, mean population per cluster: ~240

Control
n=16 clusters (population ~3800)

focal Mass Drug Administration (fMDA)
n=16 villages (population ~3800)
fMDA Flow Diagram

Informed consent confirmed (Conduct if not already done)

Yes

No

Exclude from drug administration

Confirm G6PD status (Offer test if not already done)

G6PD abnormal or declined G6PD test

- Record G6PD status on ID card
- Exclude from drug administration

G6PD normal

Exclude from drug administration:
- age <6 months old
- pregnancy (any stage)
  - known
    - identified by pregnancy test
- refusal of pregnancy test if a menstruating female and no menstruation in past 4 weeks
- breastfeeding mothers of infants with documented G6PD deficiency or unknown G6PD status
- Known hypersensitivity or adverse reaction to 8-aminoquinolines (TQ or PQ)
- currently taking mefloquine, CQ, PQ, or TQ
- retinal or visual field changes

Age <16 years old

Rounds 1a, 2a, 3a

Receive 3 day CQ+PQ

Age ≥16 years old

Rounds 1b, 2b, 3b

Receive sdCQ+PQ

Rounds 1a, 2a, 3a

Receive 3 day CQ+TQ

Rounds 1b, 2b, 3b

Receive sdCQ+TQ

Exclude from drug administration:
- pregnancy (any stage)
  - known
  - identified by pregnancy test
- refusal of pregnancy test if a menstruating female and no menstruation in past 4 weeks
- breastfeeding mothers of infants with documented G6PD deficiency or unknown G6PD status
- Known hypersensitivity or adverse reaction to 8-aminoquinolines (TQ or PQ)
- currently taking mefloquine, CQ, PQ, or TQ
- retinal or visual field changes

Hb Days 0 and 7, U/A Day 7 (with initial fMDA only)
PQ Pill count Day 7 (all years)
Outcome assessment

- Passive case detection for incidence
  - Microscopy
  - DBS in index cases pre-treatment (confirmatory PCR and sequencing if PCR+)

- Baseline, Interim, and Endline surveys – whole blood microtainers
  - PCR for parasitemia (sequencing if PCR+)
  - Microscopy in a sample
  - Serological testing

<table>
<thead>
<tr>
<th>Year (Jul-Jun)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Randomization</td>
<td>Feb</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>fMDA Round</td>
<td>1a</td>
<td>1b</td>
<td>2a</td>
<td>2b</td>
</tr>
<tr>
<td></td>
<td>Aug</td>
<td>Oct</td>
<td>Aug</td>
<td>Oct</td>
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<tr>
<td>Surveys</td>
<td>Apr</td>
<td>Aug</td>
<td>Apr</td>
<td>Aug</td>
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AE monitoring & management

- AE: Any new event, or any event present at baseline that is increasing in severity, within 14 days of drug administration

- Passive pharmacovigilance

- Active pharmacovigilance during f/u visits and during DOT for PQ

- Severity grading scale for AEs (NIAID DAIDS toxicity table) will be used

- Toxicity management will be based on standardized procedures and guidelines for withholding study drugs, follow-up tests and evaluations, and management

- Hemolytic events, other SAEs—participants receive care ≤4 hours (by helicopter if needed) to hospital in Iquitos
Questions?