FocaL mass drug **A**dministration for vivax **M**alaria **E**limination (**FLAME**)

Kick-off meeting, ASTMH 2022

Michelle Hsiang and Alejandro Llanos-Cuentas
November 2, 2022

Malaria Elimination Initiative
UCSF
University of California San Francisco

UNIVERSIDAD PERUANA CAYETANO HEREDIA

PATH

STANFORD UNIVERSITY

oucru

menzies school of health research

Universidad Cayetano Peruana Heredia (UPCH) Team

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

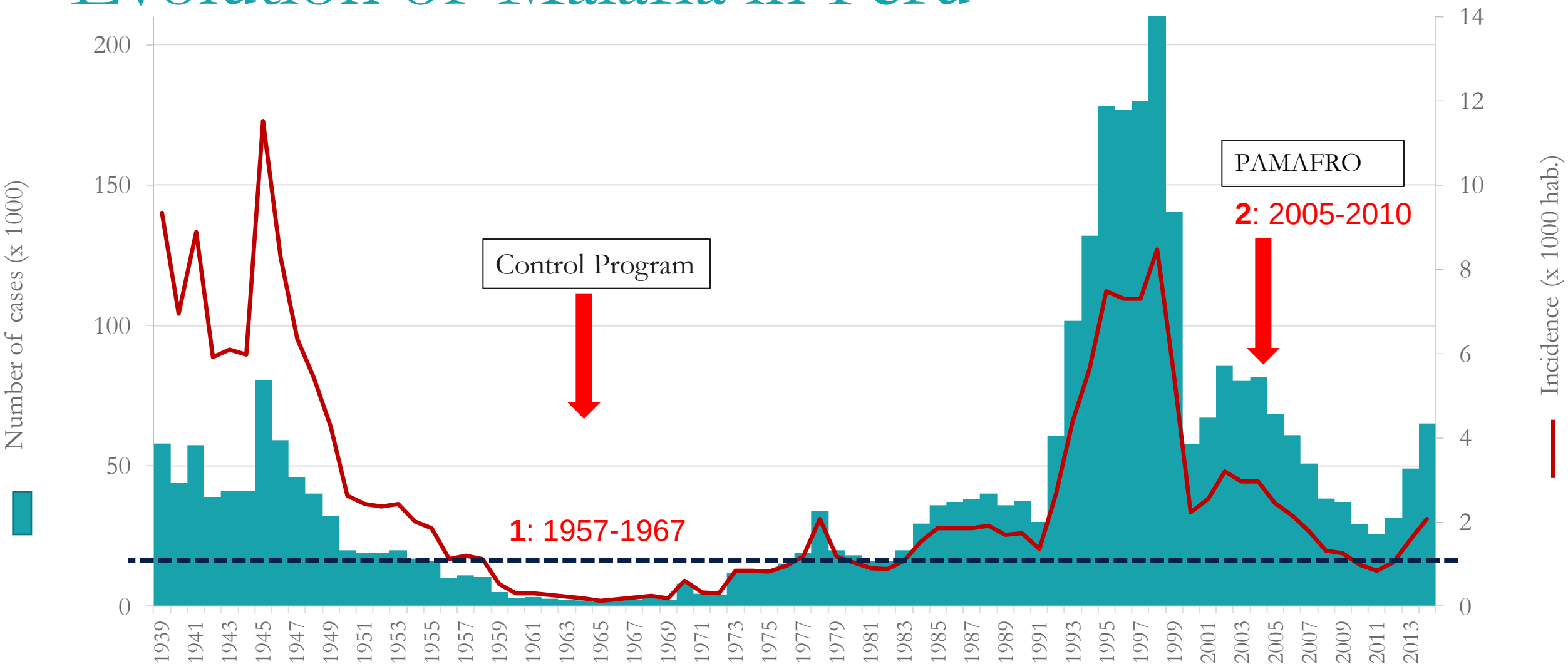
UCSF Team

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

Additional Collaborators

Institution	Name	Role
PATH	Adam Bennett, Co-I	CRCT design and analysis, geospatial analyses
	Gonzalo Domingo, Collaborator	G6PD testing
Stanford	Jade Benjamin Chung, Co-I	Trial biostatistician, spillover analyses
EOCRU	Kevin Baird, Collaborator	*P. vivax* treatment, G6PD deficiency, safety, CYP2D6
Menzies	Sarah Auburn, Collaborator	*P. vivax* genomics
	Ric Price, Collaborator	*P. vivax* treatment, G6PD deficiency, safety, *P. vivax* genomic surveillances, economic analyses

Evolution of Malaria in Peru



(1) 1954-1967, Programa Erradicación Malaria.[1965=1,500 casos]. (2) 2005-2010 PAMAFRO programa control (3) En ambos programas se alcanzó incidencias < 1 por mil

Plan Malaria Cero

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

Aprueban el Documento Técnico: "Plan Malaria Cero Período 2017-2021"

RESOLUCIÓN MINISTERIAL
Nº 244-2017/MINSA

Lima, 11 de abril del 2017

Visto el Expediente Nº 17-030023-001, que contiene la Nota Informativa Nº 369-2017-DGIESP/MINSA, de la Dirección General de Intervenciones Estratégicas en Salud Pública, y el Memorándum Nº 298-2017-DVM-SP/MINSA del Despacho Viceministerial de Salud Pública;

CONSIDERANDO:

Que, los numerales I y II del Título Preliminar de la Ley Nº 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 Nº 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 Nº 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 Nº 007-2016-SA;

SE RESUELVE:

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

Artículo 2.- Encargar a la Dirección General de

Norma Legal – Ordenanza Regional

GORELORETO

GOBIERNO REGIONAL DE LORETO

Ordenanza Regional
Nº 015-2017-GRL-CR

Villa Belén, 12 de Abril del 2017

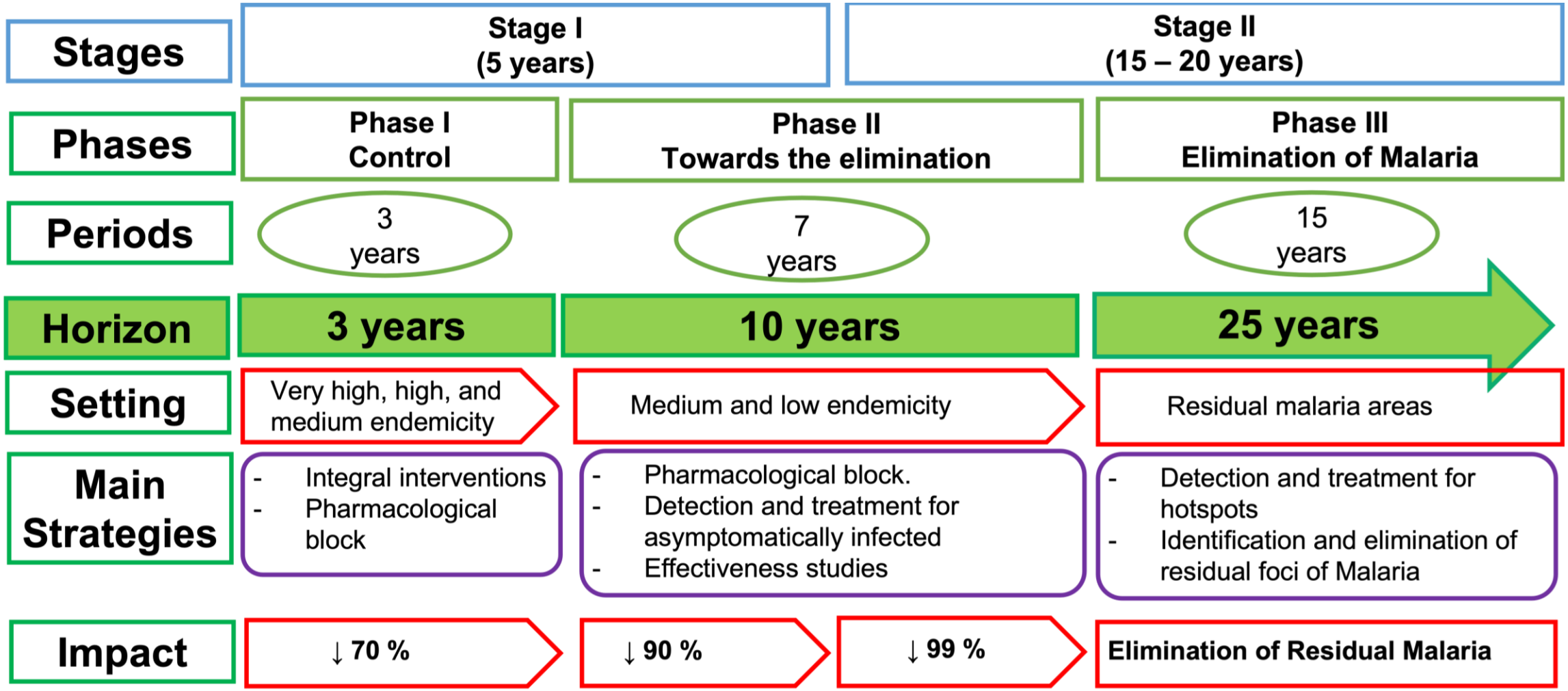
EL GOBERNADOR REGIONAL DE LORETO:

POR CUANTO:

DECLARAN COMO POLITICA PÚBLICA REGIONAL LAS CINCO POLITICAS PÚBLICAS REGIONALES DE: DISMINUCIÓN DE LA DESNUTRICIÓN CRONICA INFANTIL, ANEMIA, ELIMINACIÓN DE LA MALARIA, DISMINUCIÓN DE LA MORTALIDAD MATERNA Y EMBARAZO EN ADOLESCENTES EN LA REGIÓN LORETO.

ARTÍCULO PRIMERO: DECLARAR COMO PRIORIDAD PUBLICA REGIONAL, las CINCO POLITICAS PÚBLICAS DE SALUD REGIONALES DE: DISMINUCIÓN DE LA DESNUTRICIÓN CRONICA INFANTIL; ANEMIA; ELIMINACIÓN DE LA MALARIA; DISMINUCIÓN DE LA MORTALIDAD MATERNA y EMBARAZO EN ADOLESCENTES EN LA REGIÓN LORETO.

Plan Malaria Cero



Main Study Objectives

1. Determine the effectiveness of fMDA to reduce *Pv* 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

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

Primary & Secondary Outcomes

Aim 1

- **Cumulative incidence of Pv infection**
- Pv infection prevalence
- Pv seroprevalence
- Pv genetic diversity
- As above for Pf only, and Pf/Pv

Aim 2

- Incidence of SAE
- Incidence of severe malaria
- Incidence of any grade 3 AE or higher
- Tolerability of study drugs

Aim 3

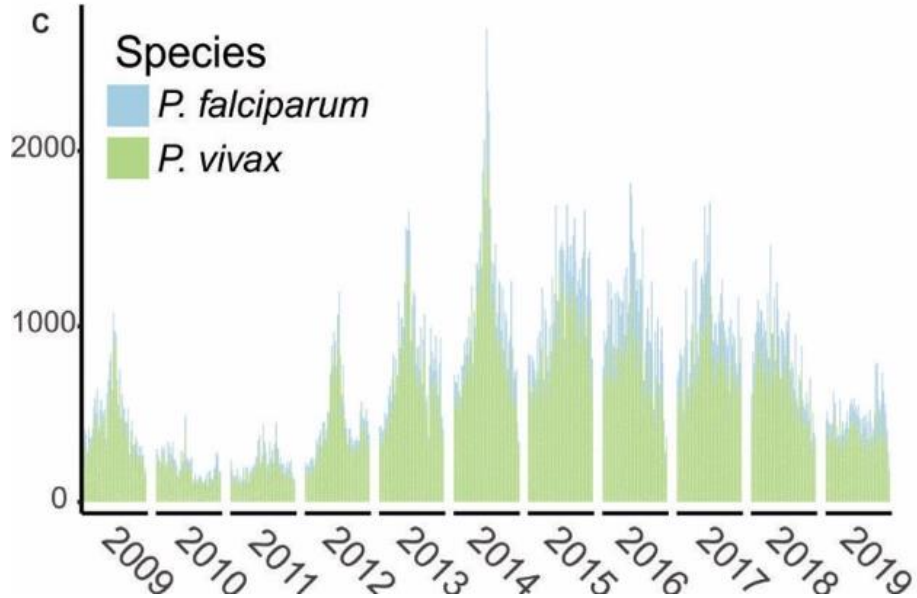
- Cost per Pv case averted or DALY, or dollar saved
- Costs per fMDA round, per capita
- Refusal rates
- Willingness to continue to participate (interim and endline surveys)

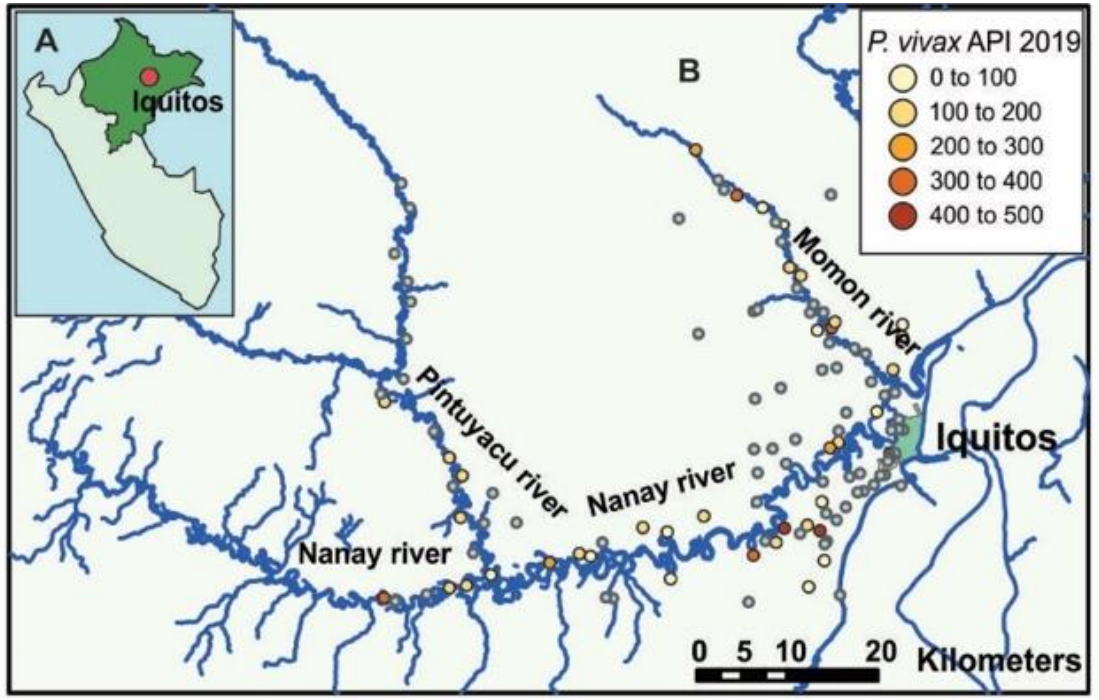
Sub-studies

- 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

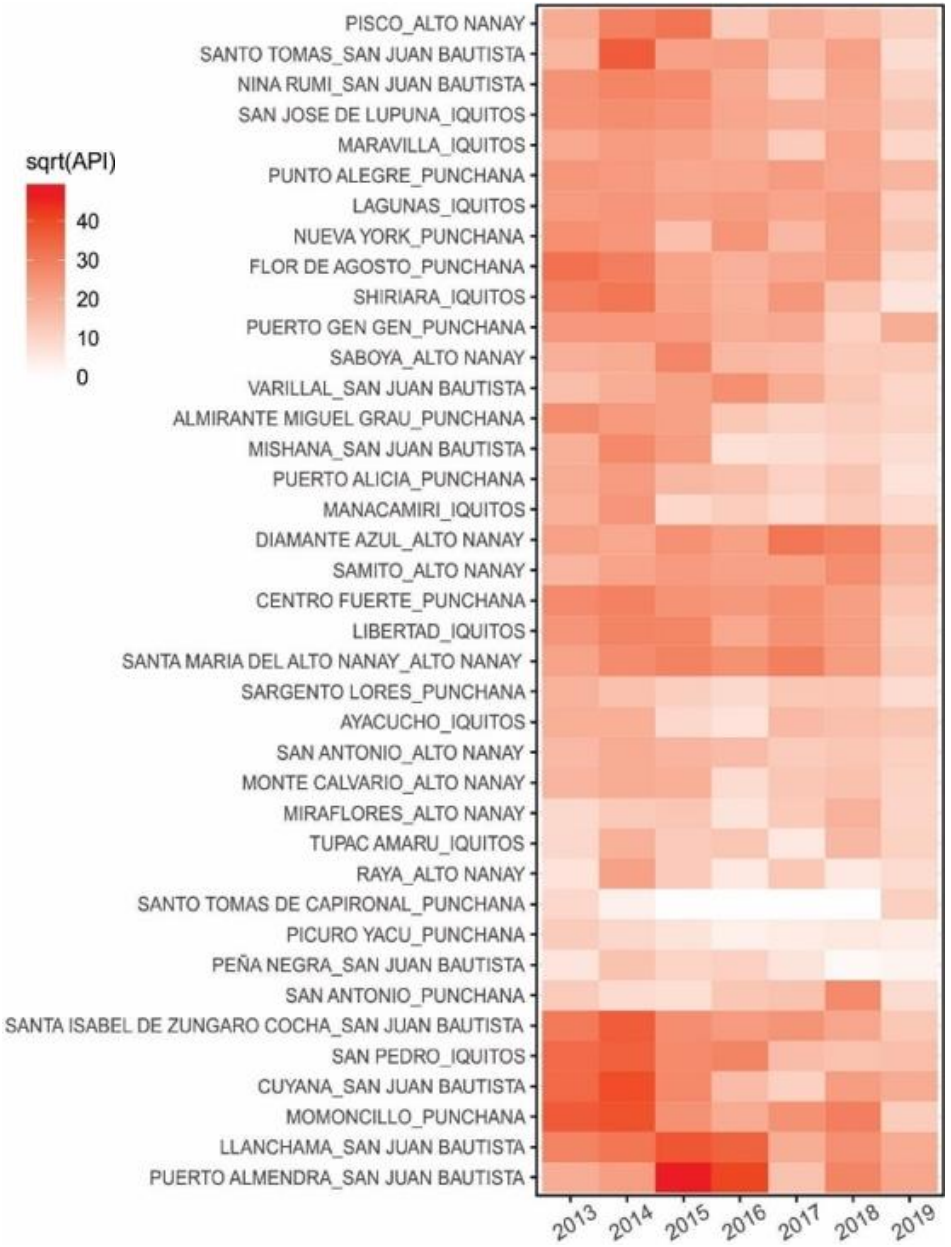
- Tropical/subtropical region of the Amazon
- Predominantly Pv
- Perennial transmission, rises between Nov–Jan, peaks in April
- 137 villages in Maynas province (banks of Momon, Nanay, and Pintuyacu Rivers)
  - 4 districts: Alto Nanay, Iquitos, Punchana, and San Juan Bautista
- Prevalence of Pv blood 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

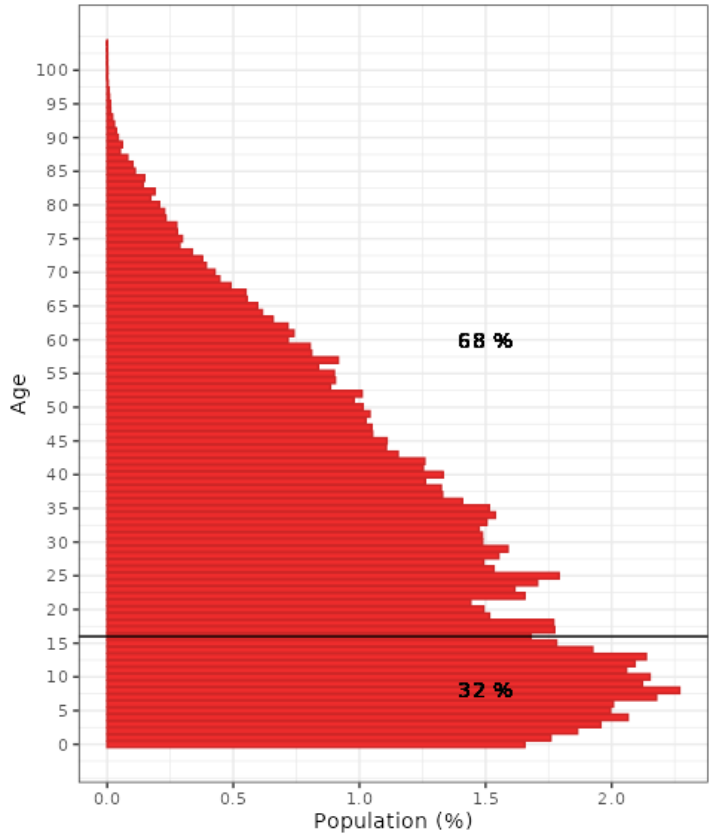


Annual parasite incidence (API) by year in 39 clusters eligible for randomization.

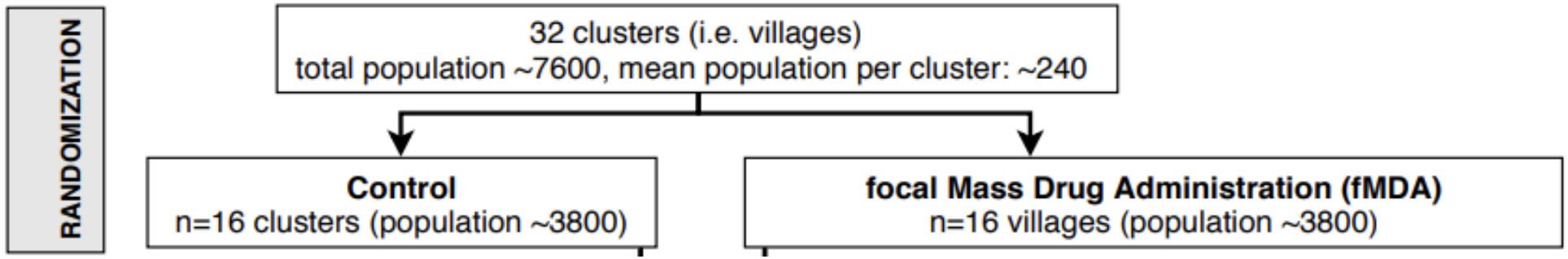
Interventions

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

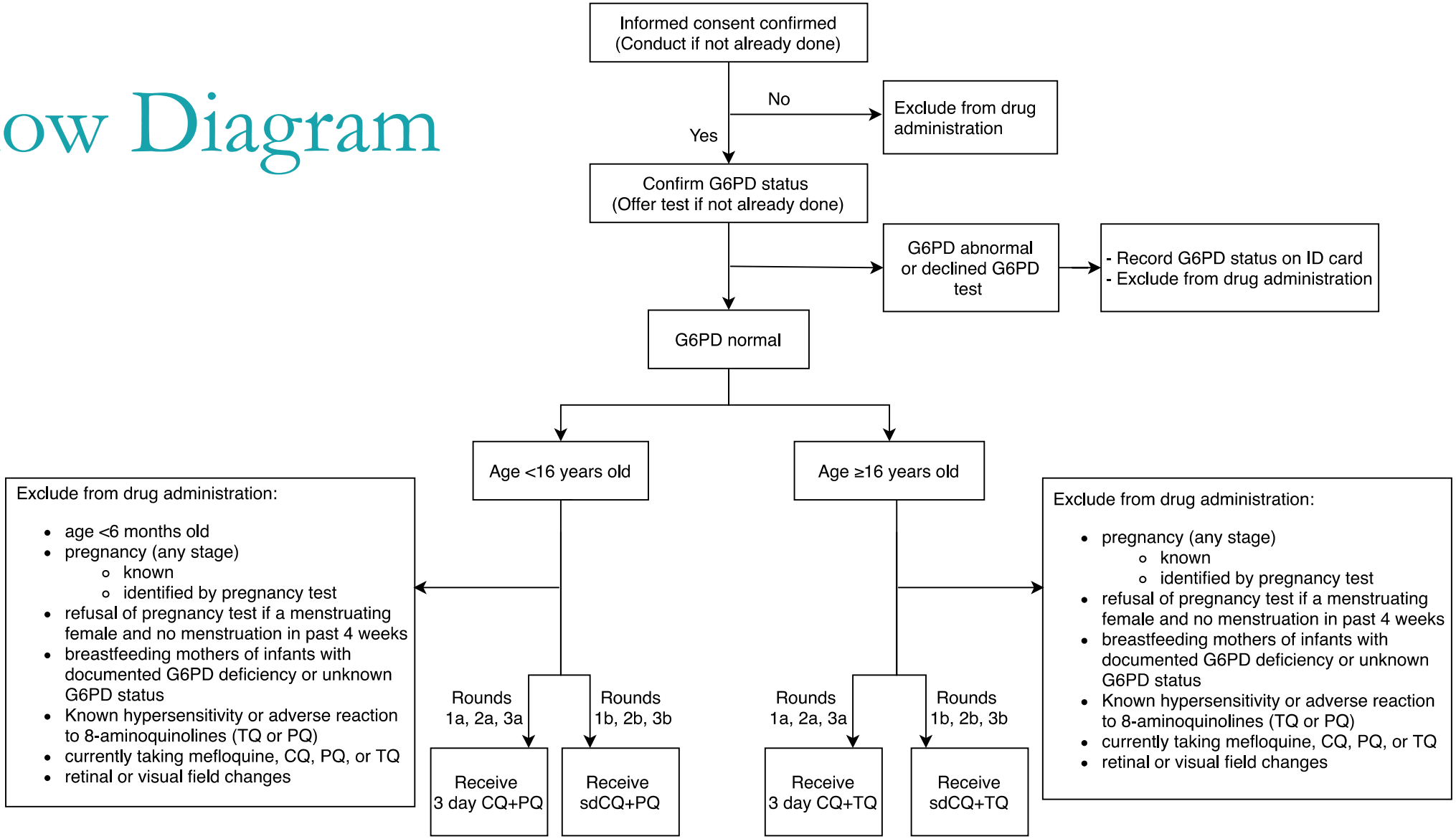
- **fMDA prior to high season by DOT**
  - Rounds 1 - August
    - ≥ 16 years: **3 day CQ** (10/10/5 mg/kg) + **TQ** (300 mg)
    - 6 mos - 16 years: **3 day CQ** (10/10/5 mg/kg) + **PQ** (3.5 mg/kg over 7d)
  - Rounds 2 – October
    - ≥ 16 years: **single dose CQ** (10 mg/kg) + **TQ** (300 mg)
    - 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



fMDA Flow Diagram



fMDA follow-up:
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

Year (Jul-Jun)	1		2			3			4		
Randomization	Feb										
fMDA Round			1a Aug	1b Oct		2a Aug	2b Oct		3a Aug	3b Oct	
Surveys		Apr	Aug		Apr	Aug		Apr	Aug		Apr

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?