

Malaria Molecular Surveillance Study Design Workshop

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MRC Centre for Global Infectious Disease Analysis

WHO Collaborating Centre for Infectious Disease modelling

*School of Public Health
Imperial College London*

Welcome!

- No fire alarms planned
- Restrooms
- WIFI: Network **Aloft**, no password
- Check in and breakfast vouchers
- Teas, Coffees, refreshments

Acknowledgements



MRC Centre for
Global Infectious
Disease Analysis

IMPERIAL

BILL & MELINDA
GATES *foundation*

Demonstrators: Dr. Gina Cuomo-Dannenburg and Dr. Sequoia Leuba

Guest lecture: Hinda Doucoure

What is Malaria Molecular Surveillance (MMS)?



Genomic epidemiology: the study of the genetic characteristics of pathogens to understand their transmission, distribution, and evolution. Combines genetic data with epidemiological information to improve our understanding of disease.

Genomic surveillance: the systematic, ongoing collection and analysis of pathogen genetic data to monitor for genetic changes that could impact public health. Focuses on actionable information and impacts on control.

High priority areas for surveillance

1. Monitoring the prevalence of established molecular markers of drug resistance (*crt*, *dhfr*, *dhps*, *mdr1*).
2. Detecting the emergence of rare variants of concern and tracking their spread in space and time (e.g. *k13*).
3. Measuring the prevalence of *hrp2/3* gene deletions as part of decision frameworks that directly impact control strategies.

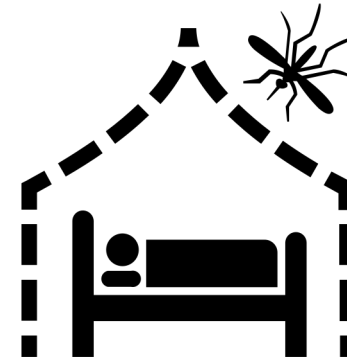
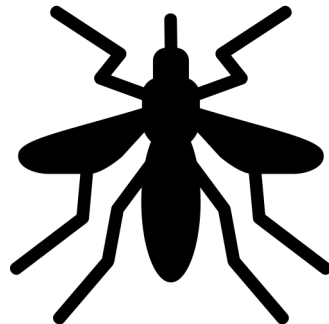
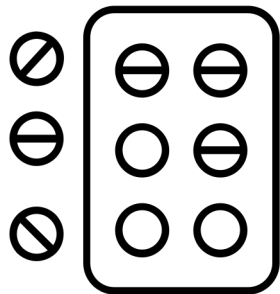
Other applications of MMS

1. Detect imported vs. locally acquired cases
2. Measure migration and connectivity between populations
3. Estimate transmission chains and networks
4. Measure changes in transmission (e.g. impact of interventions)
5. Classifying infections as reinfection, recrudescence, and relapse (vivax)

What is Malaria Molecular Surveillance (MMS)?

Other things we will NOT cover here

1. Therapeutic Efficacy Studies (TES)
2. Vector surveillance/genomics
3. Study designs for measuring interventions, e.g. clinical trials



Current state of play

Monitoring markers of drug resistance



Chloroquine

pfcr

CVIET haplotype, K76T

SVMNT haplotype, A220S

Sulfadoxine- Pyrimethamine (SP)

pfdhps

A437G, K540E, A581G

pfdhfr

N561I, C59R, S108N, I164L

Mefloquine and Lumifantrine

pfmdr1

N86Y, Y184F, D1246Y

Monitoring markers of drug resistance

pfcr

- Historically (pre-2000) at high prevalence, following intense use of chloroquine
- Decline in some places following switch to ACTs
- Current distribution is patchy

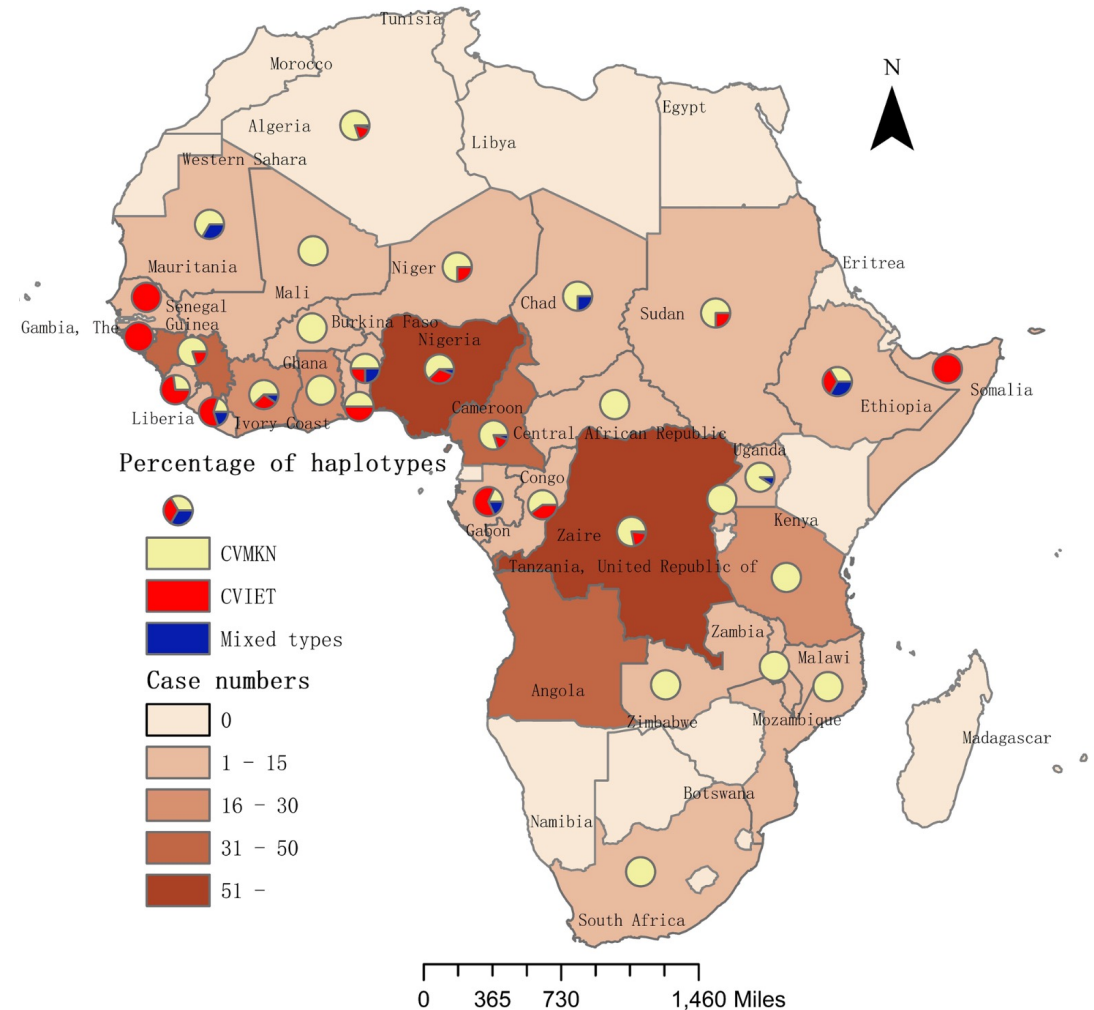
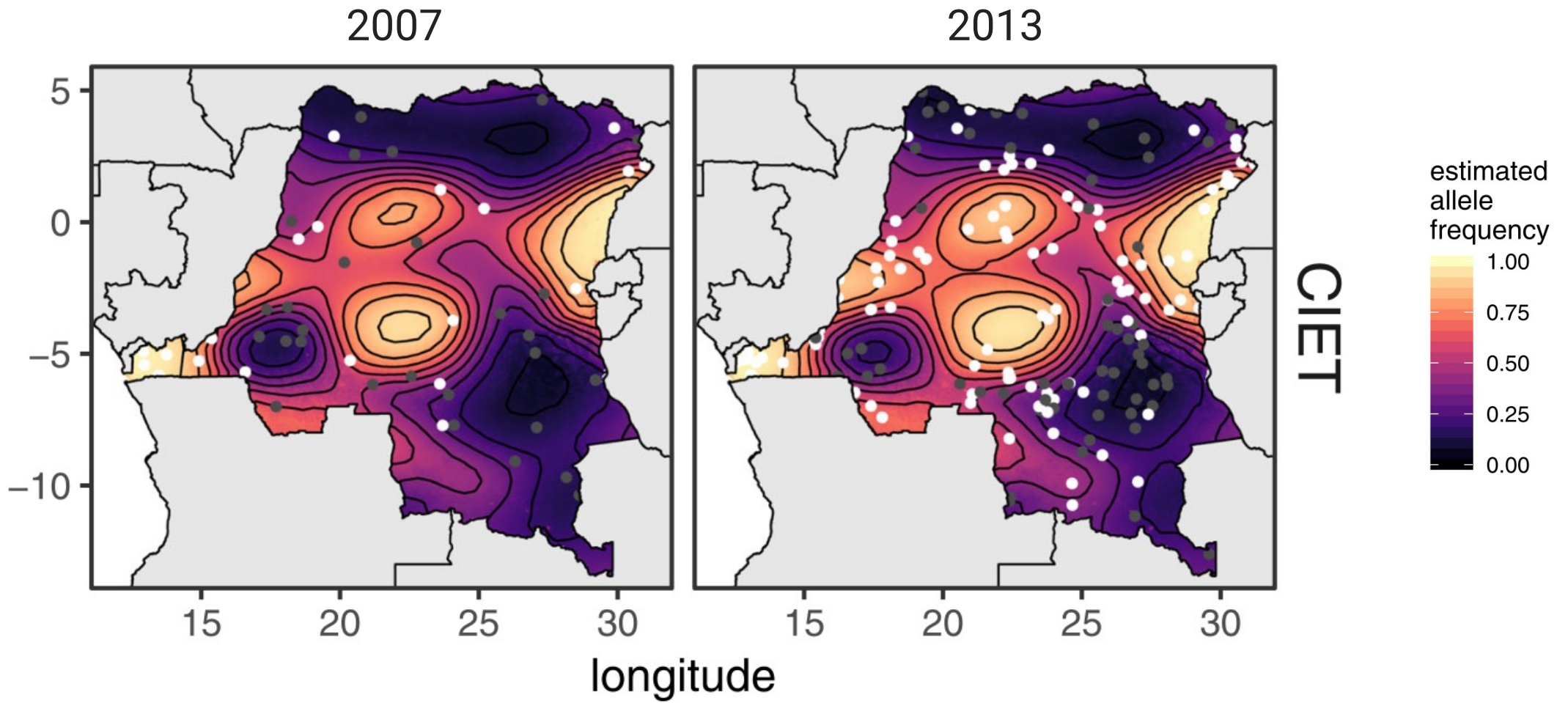


Fig. 1 The number of imported *P. falciparum* cases from Africa and percentage of haplotypes of *Pfcr*

Monitoring markers of drug resistance

pfcrt

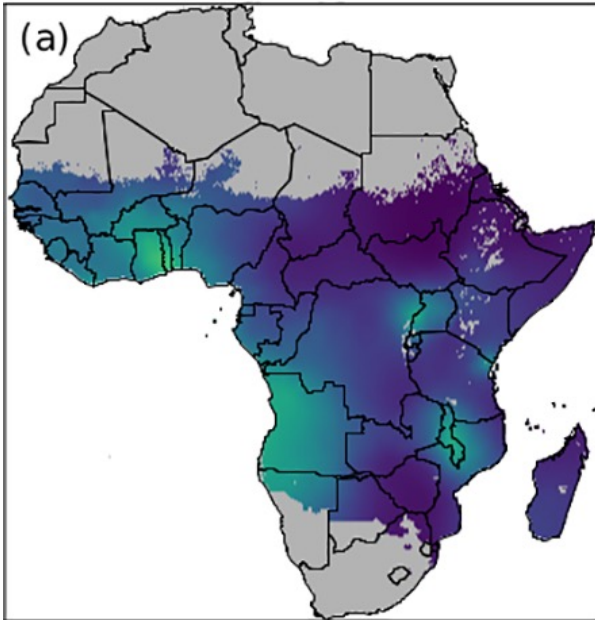
Democratic Republic of the Congo



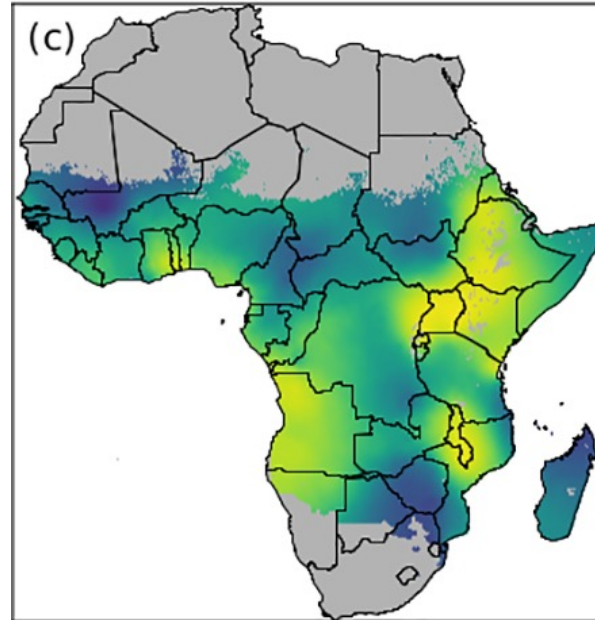
Monitoring markers of drug resistance

pfdhps A437G

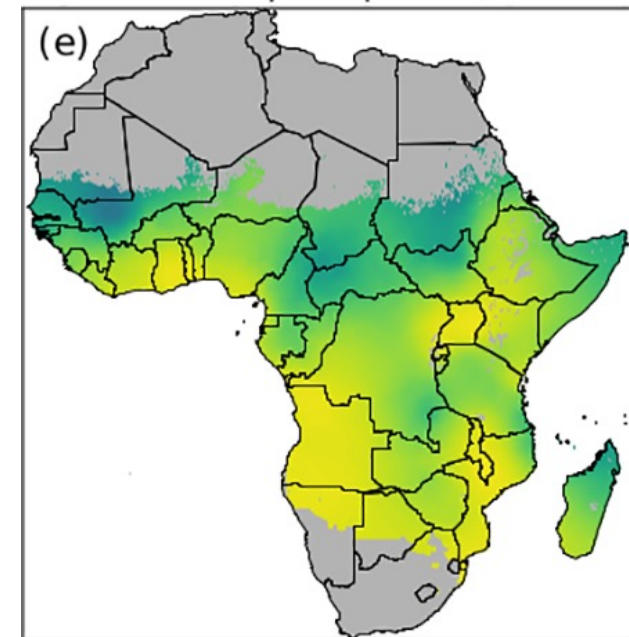
Median map: dhps437, 1990



Median map: dhps437, 2005



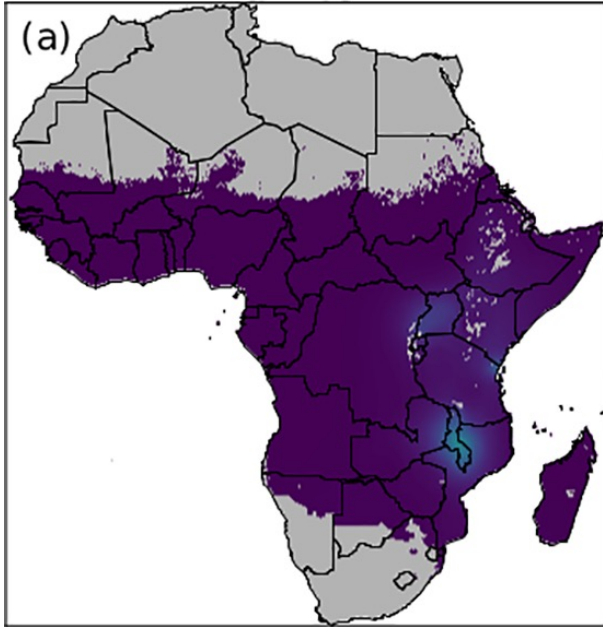
Median map: dhps437, 2020



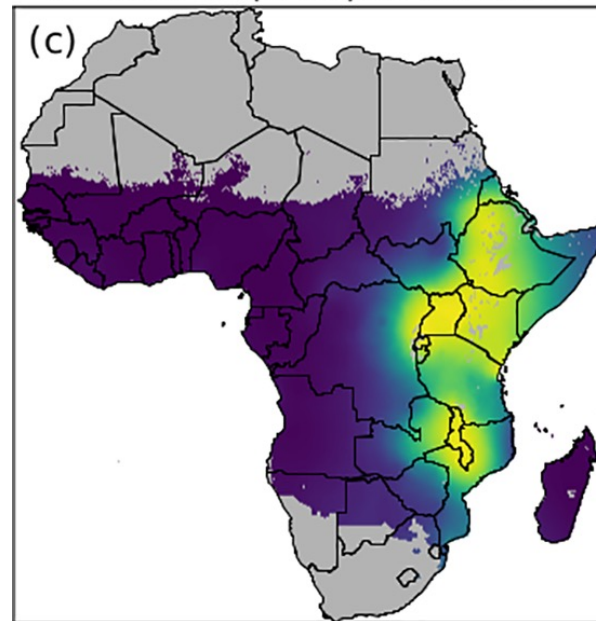
Monitoring markers of drug resistance

pfdhps K540E

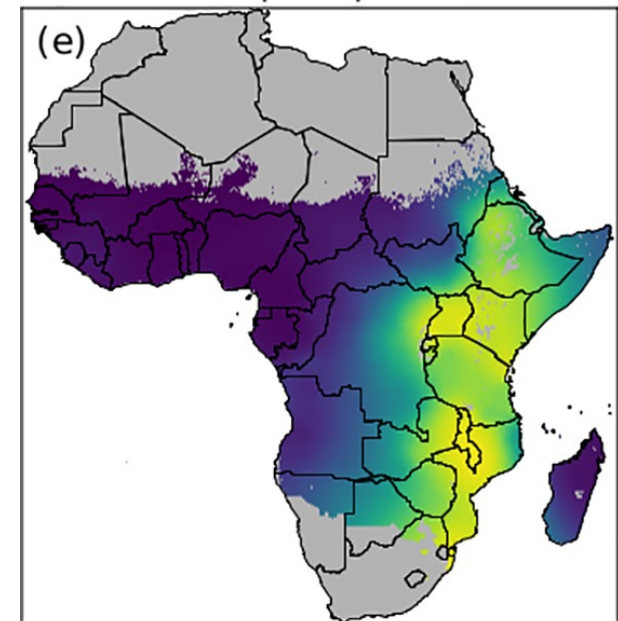
Median map: dhps540, 1990



Median map: dhps540, 2005

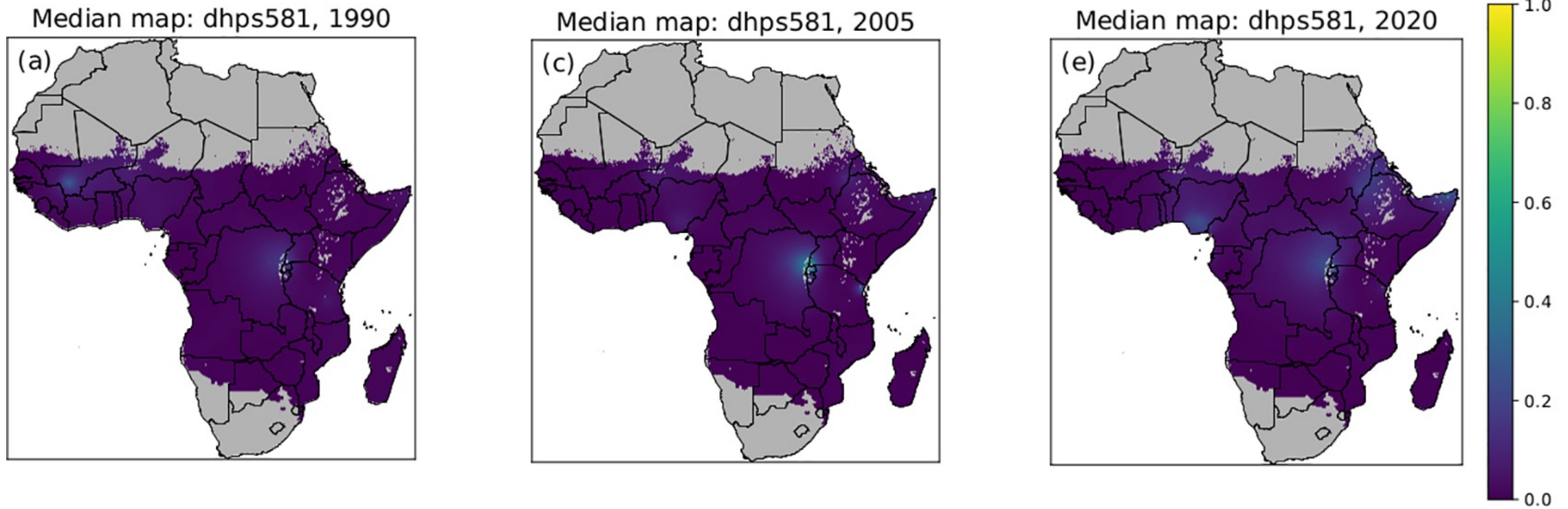


Median map: dhps540, 2020



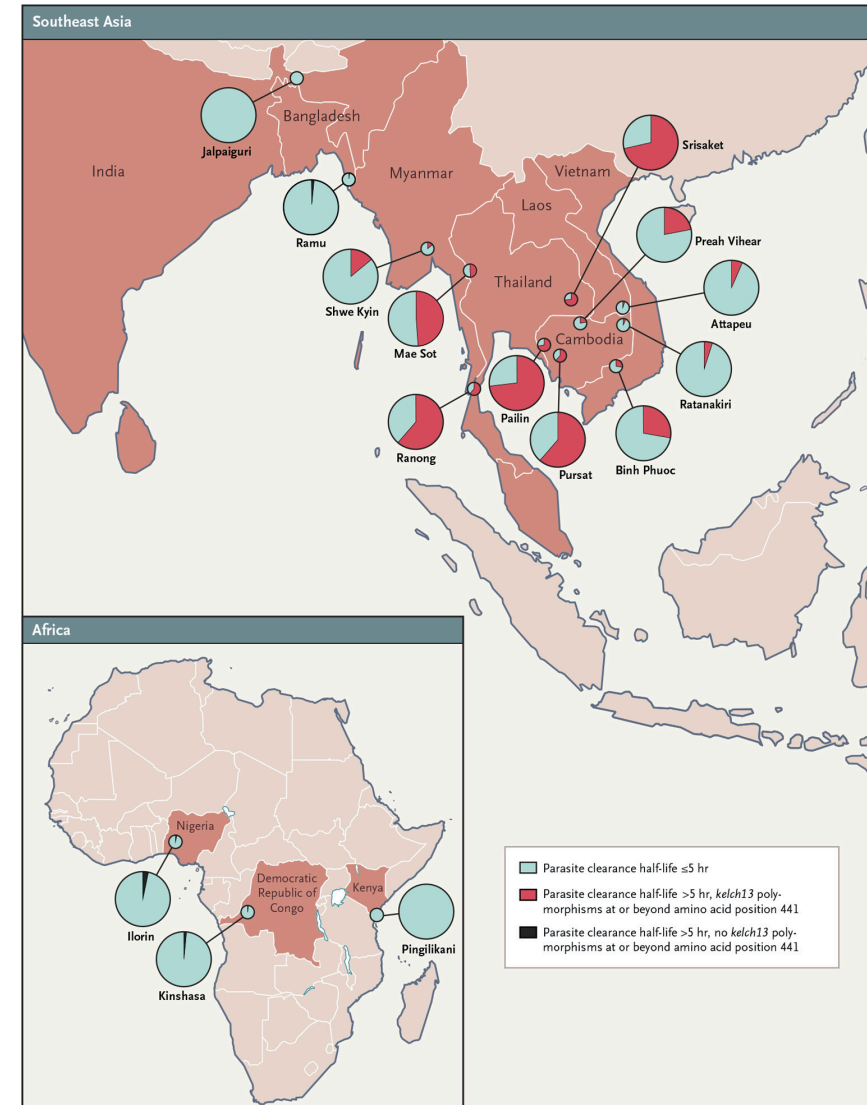
Monitoring markers of drug resistance

pfdhps A581G



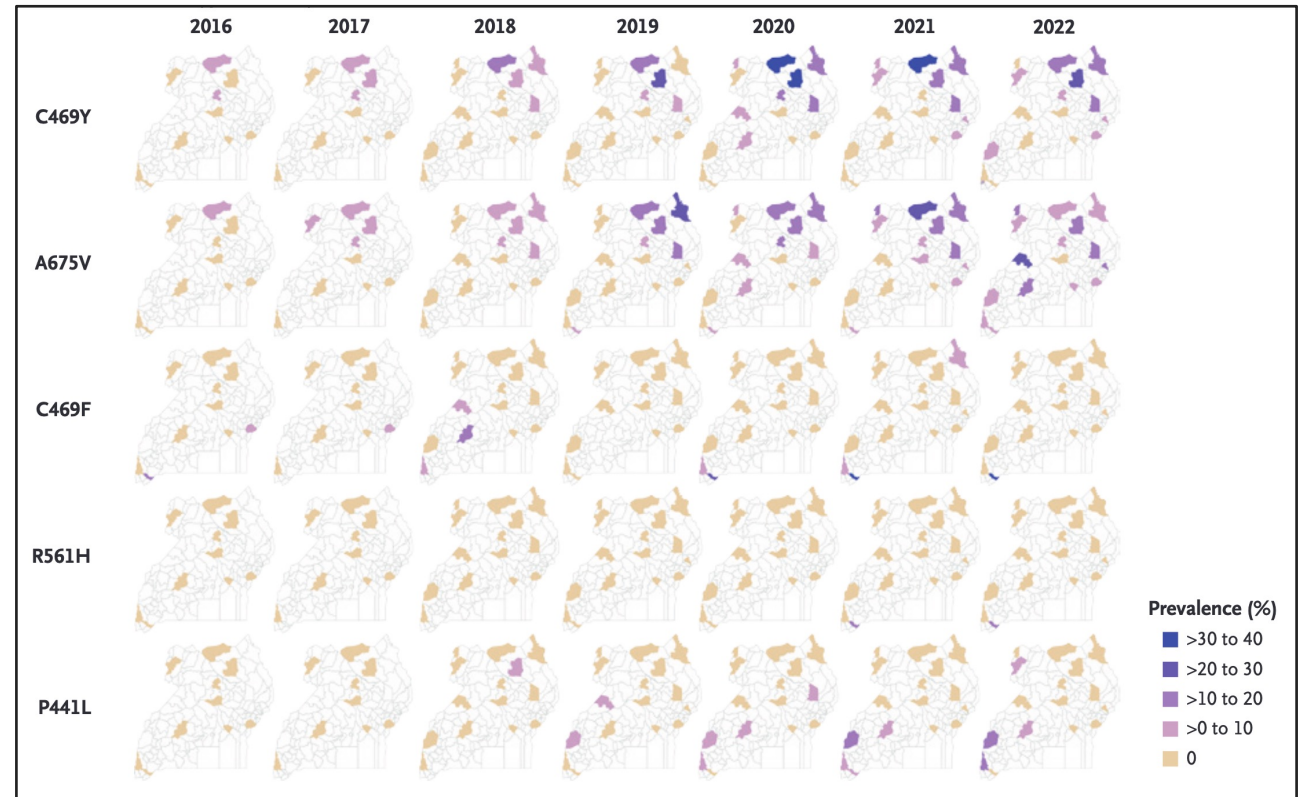
Detecting *pfk13* variants

- Delayed parasite clearance following artemisinin treatment, Western Cambodia (2000s)
- Identification of *kelch* 13 domain (2013)
- High prevalence of delayed clearance, and strong association with *pfk13* (2014)



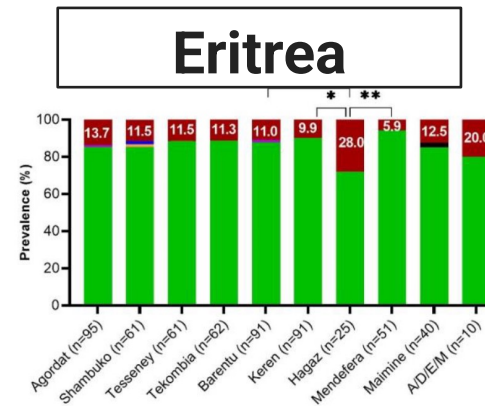
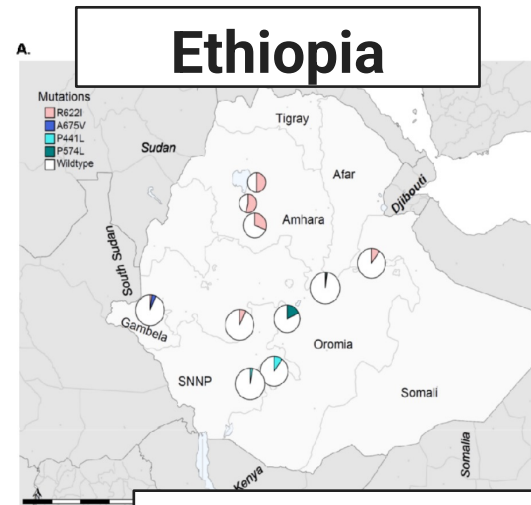
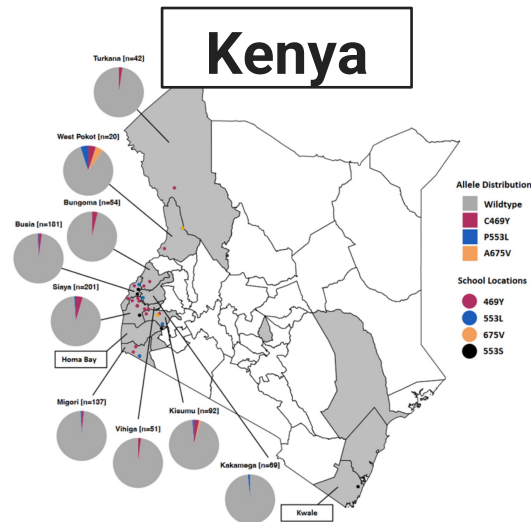
Detecting *pfk13* variants

- Enhanced survival of parasites after *in vitro* artemisinin exposure in Northern Uganda (2018)
- In Rwanda, *pfk13* mutations found to have increased between 2015 and 2018
- Spread in space and time from Northern Uganda (2023)

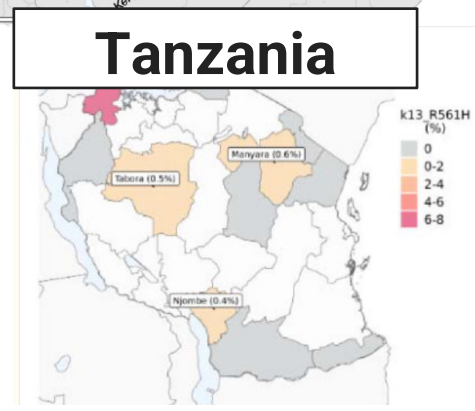
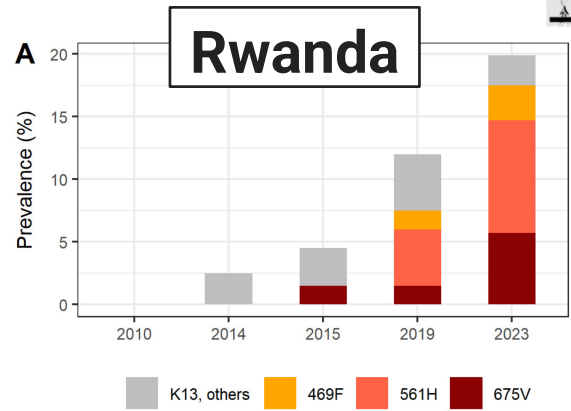
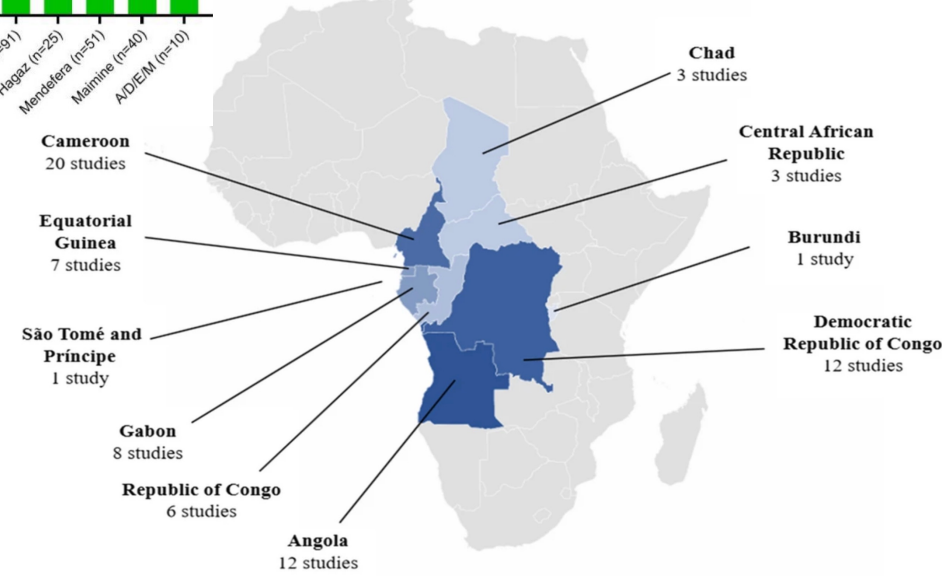


Detecting pfk13 variants

pfk13 mutations now found throughout Sub-Saharan Africa

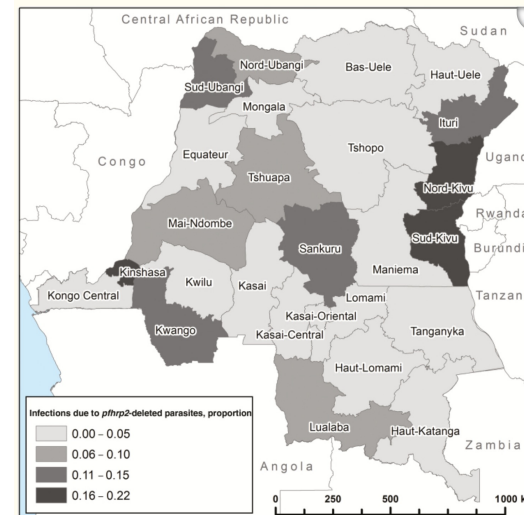
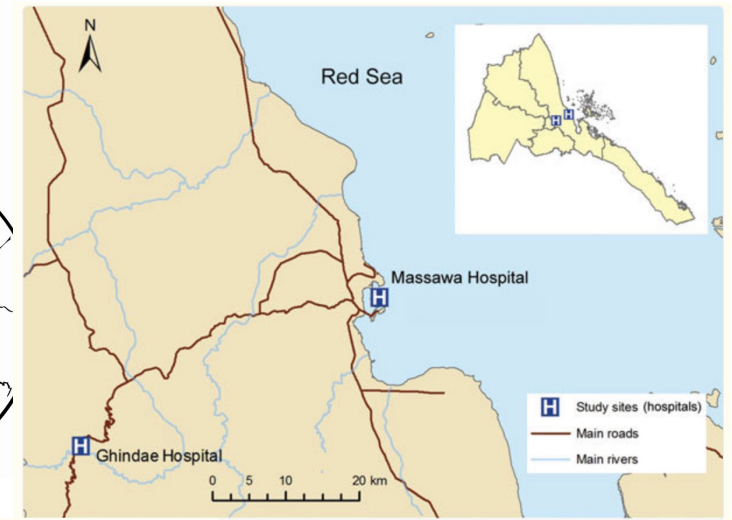
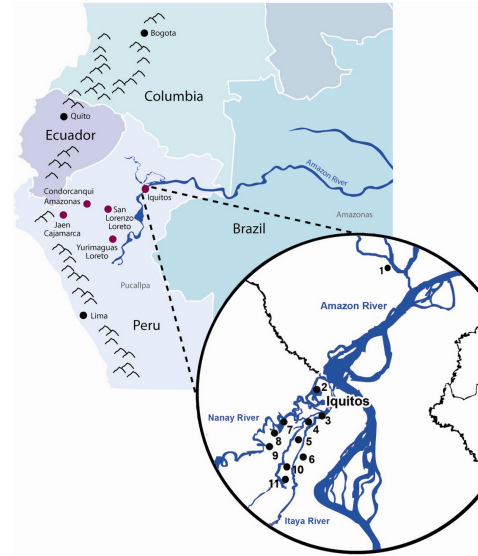


Central Africa



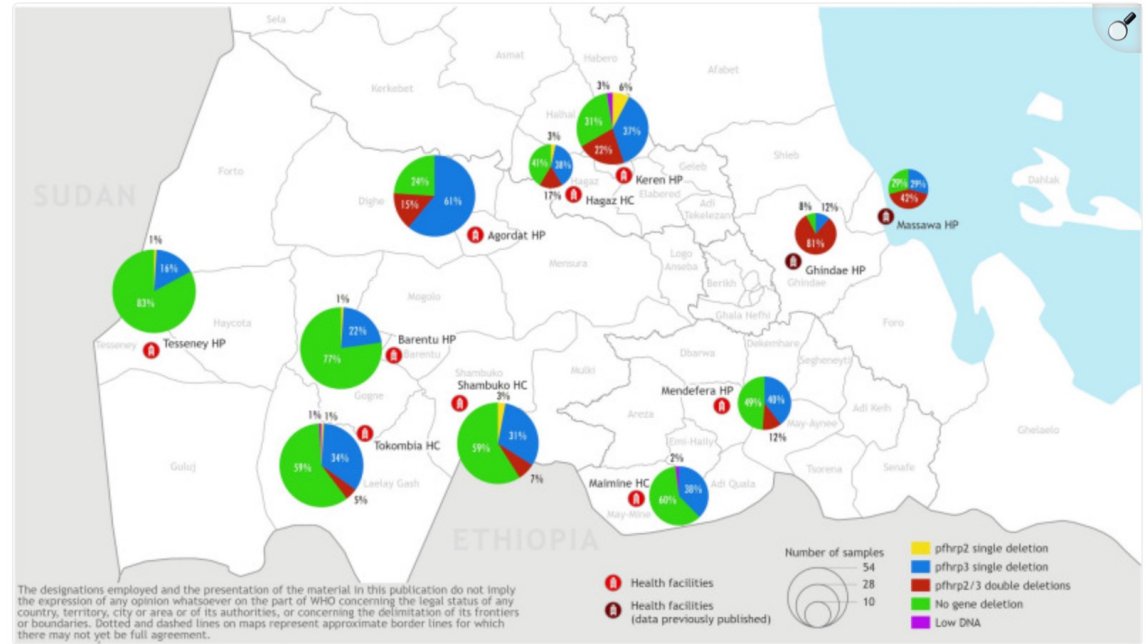
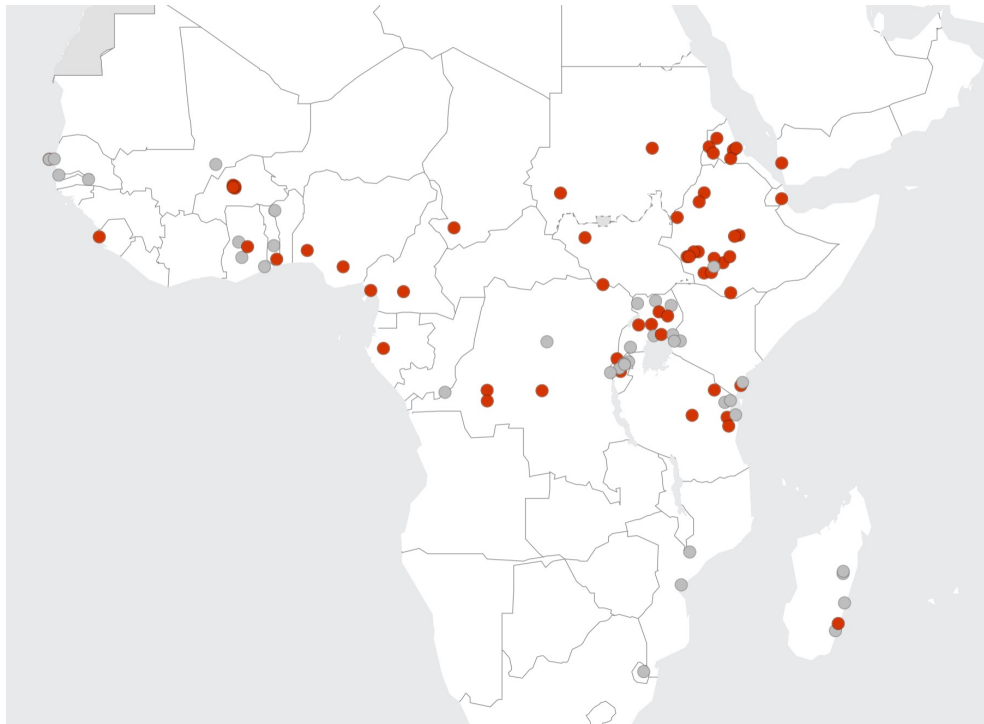
Identifying and quantifying *pfhrp2/3* deletions

- First reports in Peru in 2010
- Turning point in 2016, identification in Eritrea and India
- Similar time (2017) identification in DRC from large cross-sectional surveys
- Moderate prevalence in Kenya, scattered prevalence in Mozambique and Tanzania



Identifying and quantifying *pfhrp2/3* deletions

Pfhrp2/3 deletions now found throughout Sub-Saharan Africa, and at high prevalence in the Horn of Africa



Partner drug resistance

Patchy distribution throughout SSA. Some markers close to fixation, others spreading or receding

Artemisinin resistance

Distinct epicenters in Northern Uganda and the Horn of Africa

pfhrp2/3 deletions

High prevalence in the Horn of Africa, identified throughout SSA

Back to study design

How does study design come into this

Major changes in MMS...

- Scale-up in number of sites and samples
- Deeper and wider sequencing
- Changes in distribution of genomic infrastructure

Few general guidelines on...

- Study structure
- Minimum sample size
- Type of sequencing technology
- Which analysis tools to use

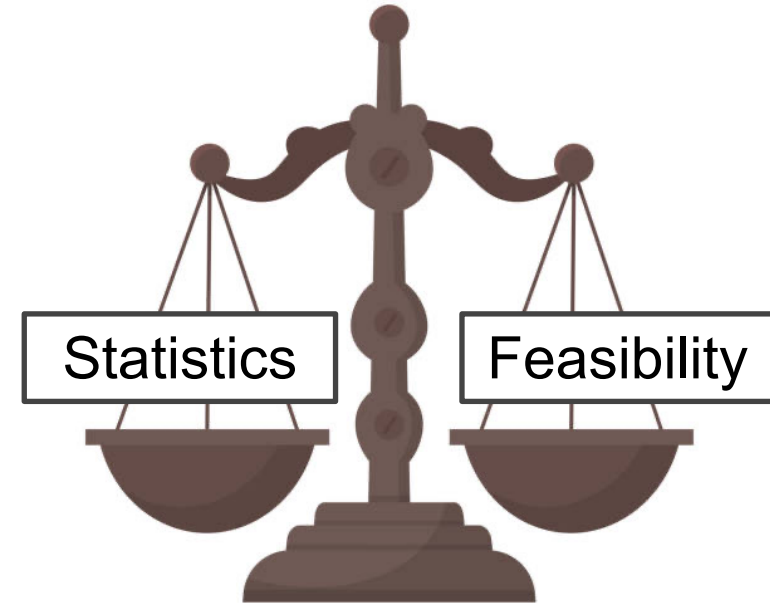


Strengthen our statistical plans

- Precision and confidence intervals
- Power analysis
- Sample size calculation
- More advanced tools

Put this in real world context

- Combine statistics with logistics, feasibility, budget etc.
- Discuss challenges and share solutions
- Identify areas for future development



Monday

- **M1:** Sampling from a population
- **M2:** Sample size based on precision
- Structured discussion: experiences and challenges

Dinner at Antoinettes



Tuesday

- Guest lecture: Hinda Doucoure
- **M3:** Hypothesis testing and power
- **M4:** Multi-cluster studies
- **Lunch**
- **M5:** The DRpower tool
- **M6:** Designing studies for multiple endpoints
- Structured discussion: Future steps

We want to hear from you!

- Name
- Affiliation
- Your reasons for attending this workshop