Malaria Molecular Surveillance Study Design Workshop

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IMPERIAL

Welcome!

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.

What is Malaria Molecular Surveillance (MMS)?

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.

What is Malaria Molecular Surveillance (MMS)?

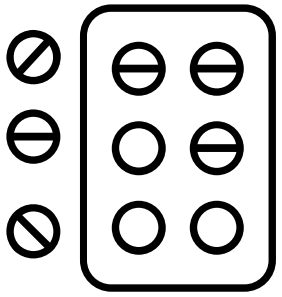
Other applications of MMS

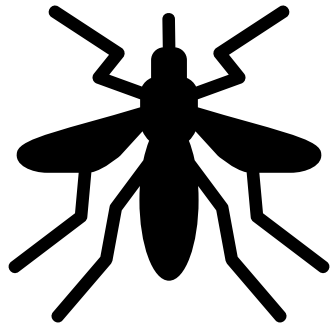
1. Detect imported vs. locally acquired cases
2. Measure migration and connectivity between populations
3. Estimate transmission chains and networks
4. Measure changes in transmission (e.g. impact of interventions)
5. Classifying infections as reinfection, recrudescence, and relapse (vivax)

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	*pfcrt*	*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

pfcrt

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

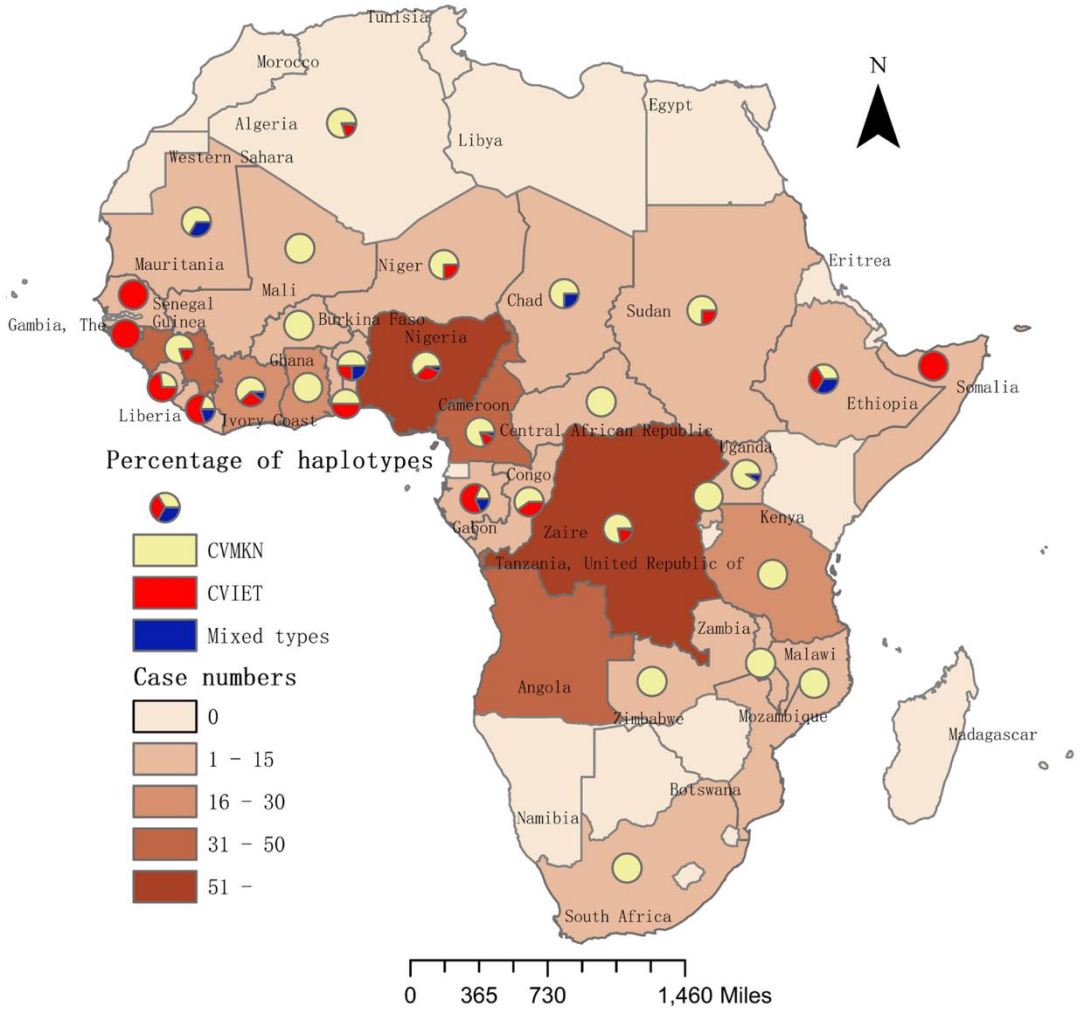
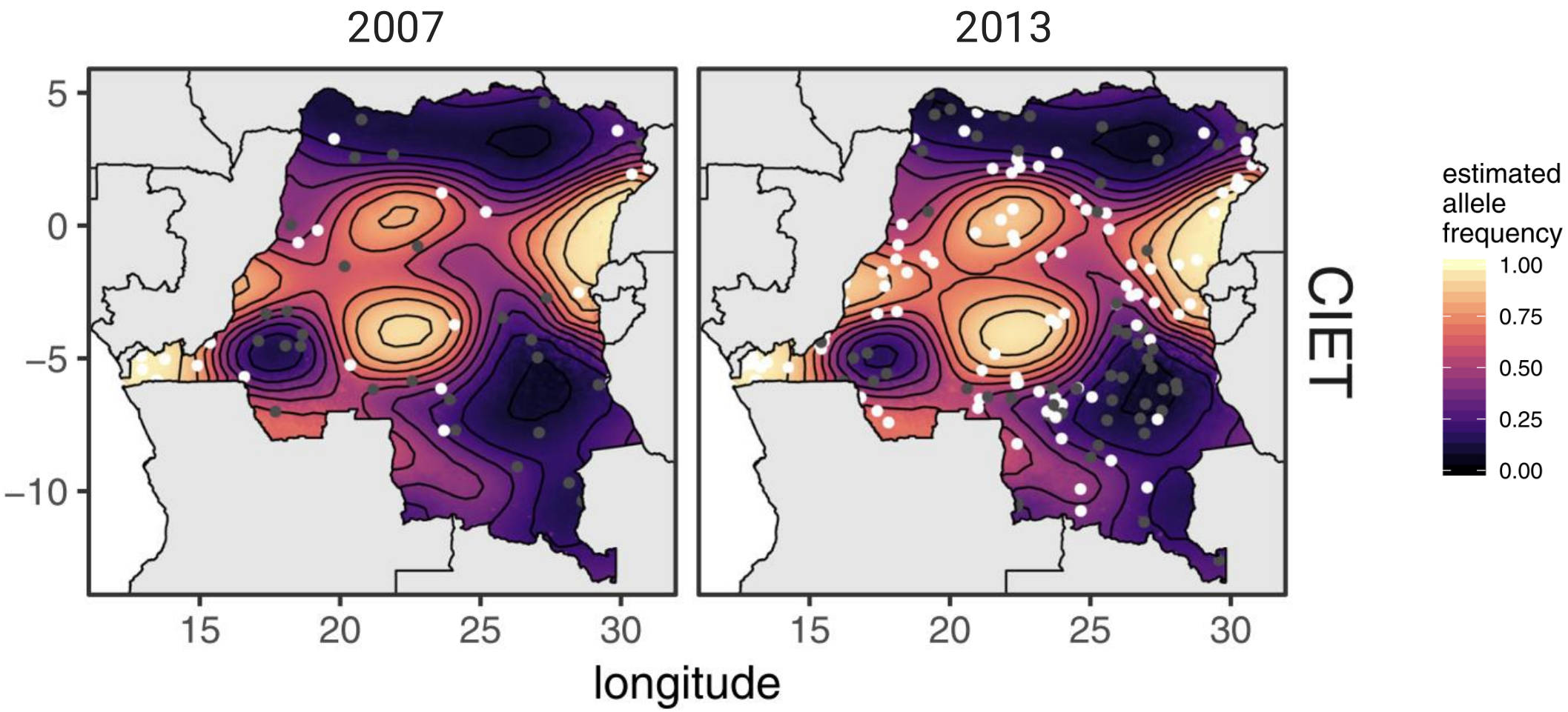


Fig. 1 The number of imported *P. falciparum* cases from Africa and percentage of haplotypes of *Pfcrt*

Monitoring markers of drug resistance

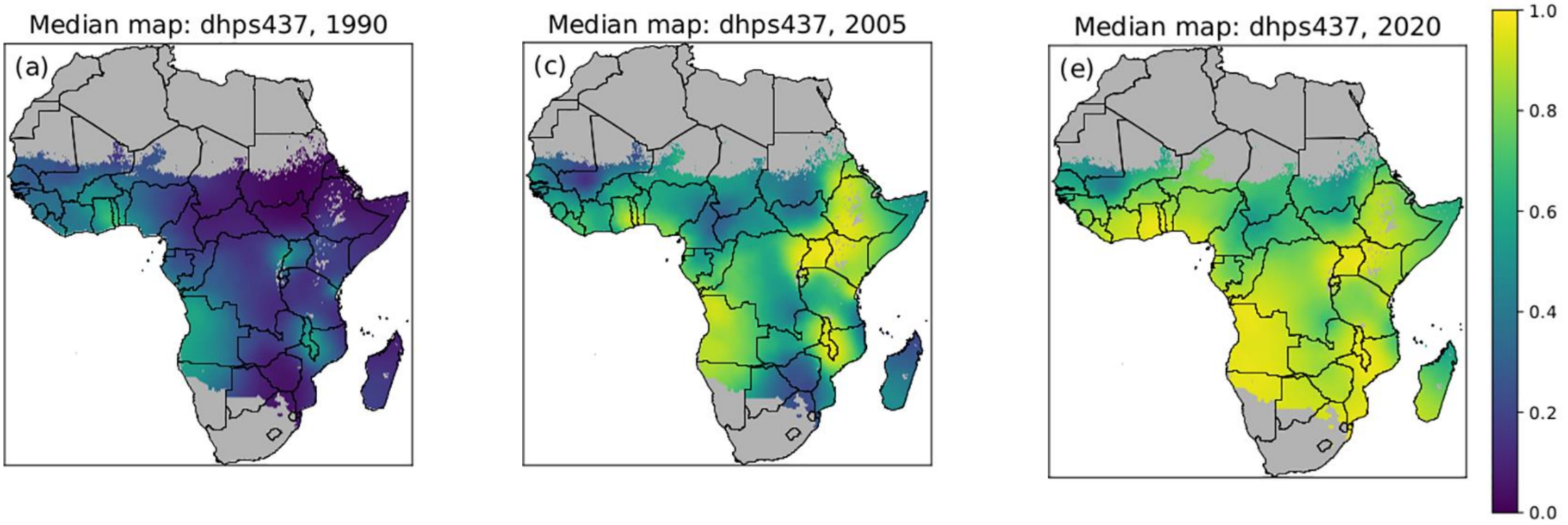
pfcrt

Democratic Republic of the Congo



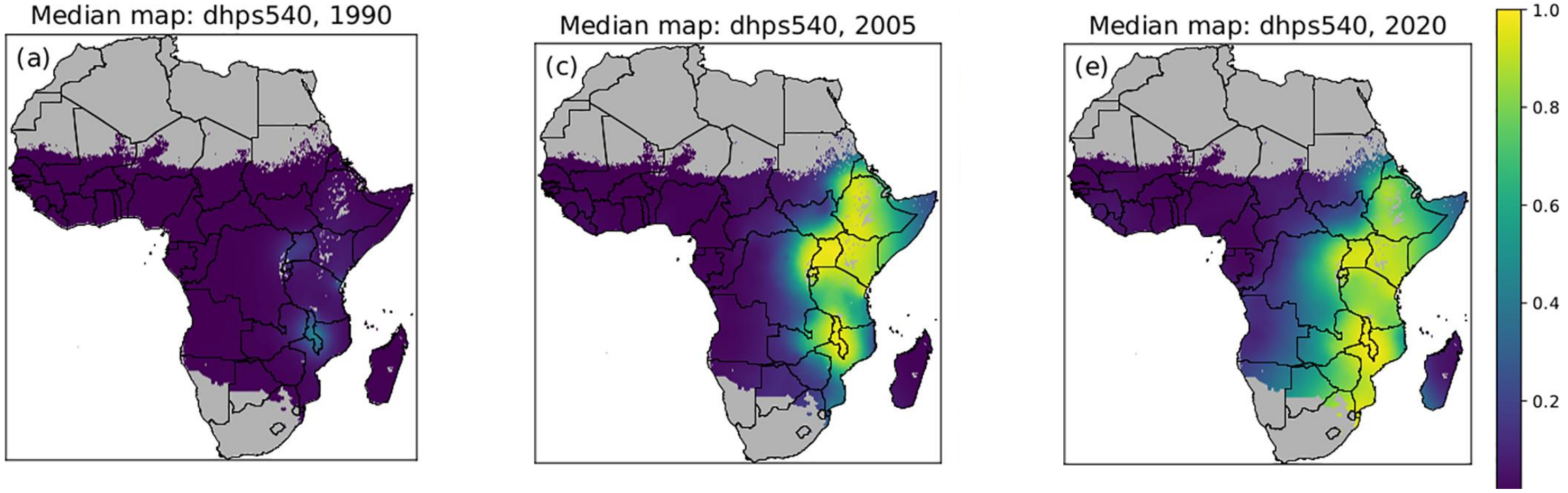
Monitoring markers of drug resistance

pfdhps A437G



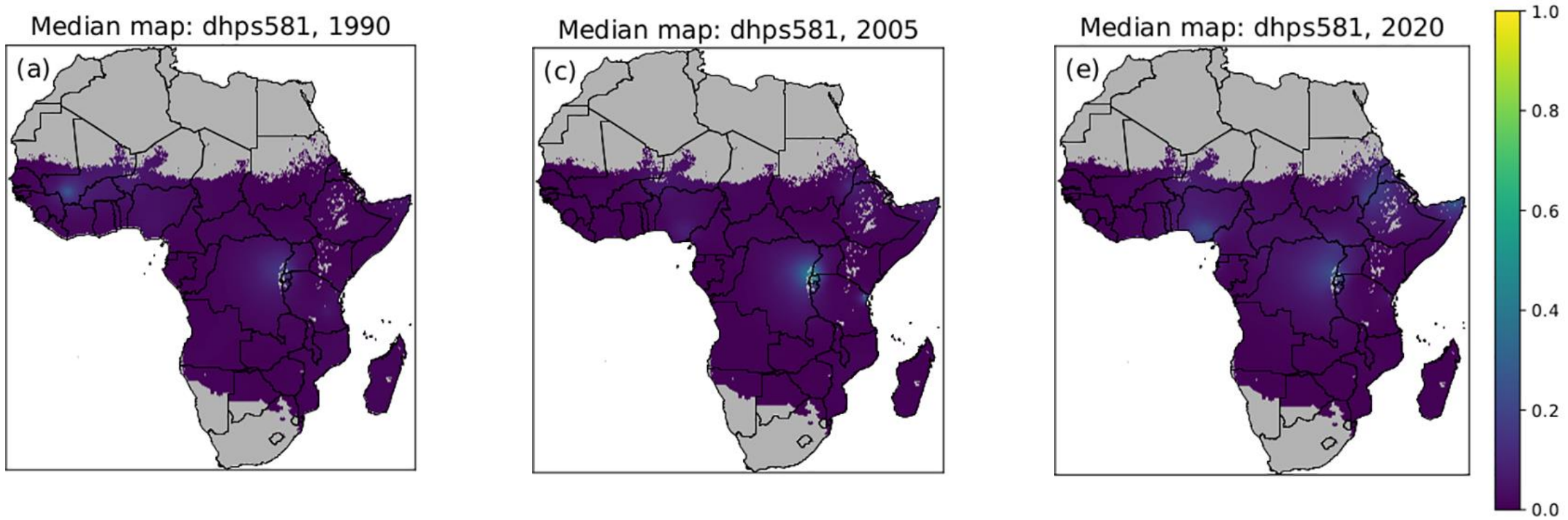
Monitoring markers of drug resistance

pfdhps K540E



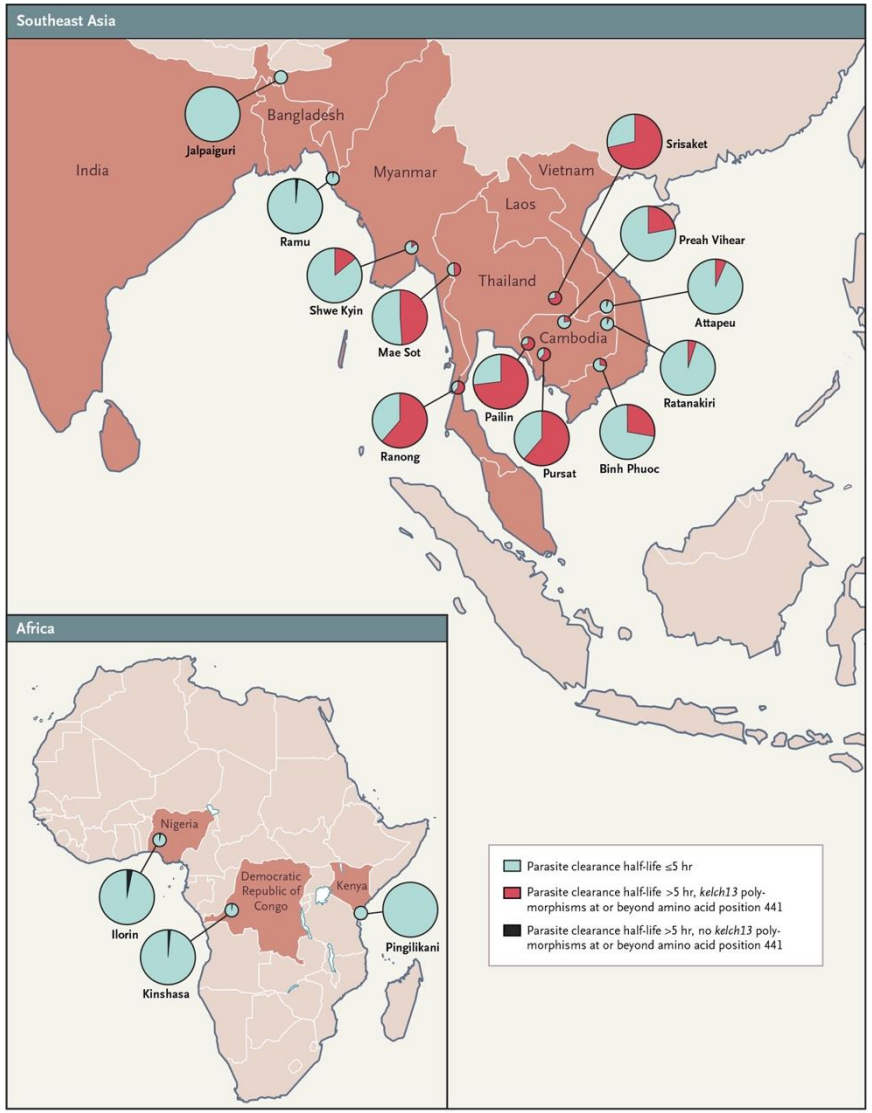
Monitoring markers of drug resistance

pfdhps A581G



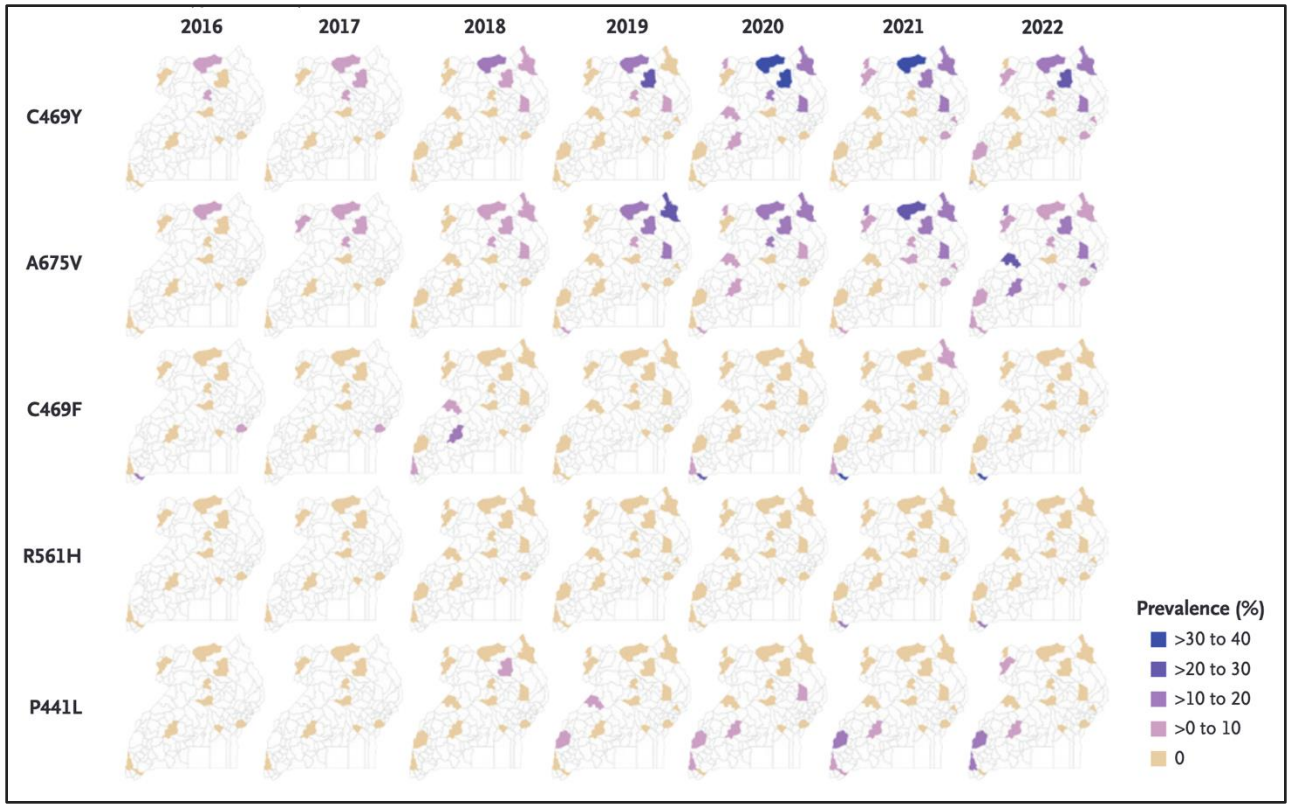
Detecting pfk13 variants

- 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

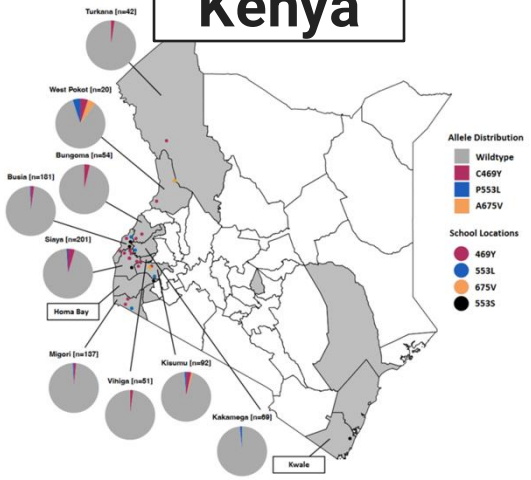
- Enhanced survival of parasites after *in vitro* artemisinin exposure in Northern Uganda (2018)
- In Rwanda, *pfk13* mutations found to have increased between 2015 and 2018
- Spread in space and time from Northern Uganda (2023)



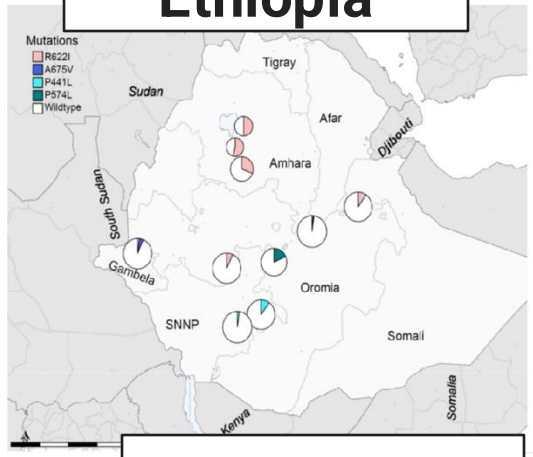
Detecting pfk13 variants

pfk13 mutations now found throughout Sub-Saharan Africa

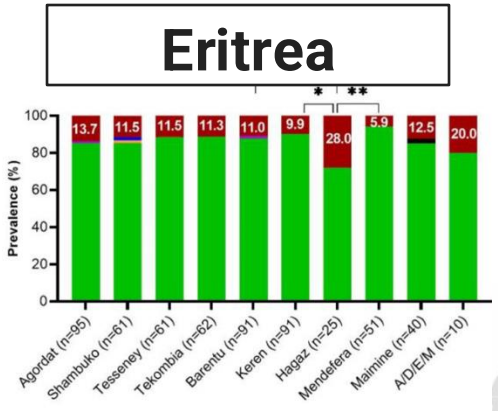
Kenya



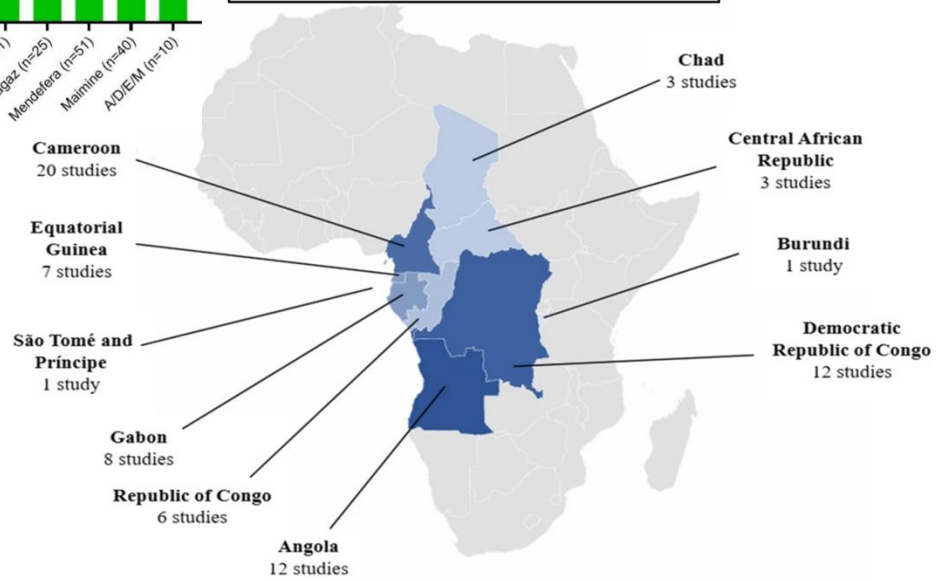
Ethiopia



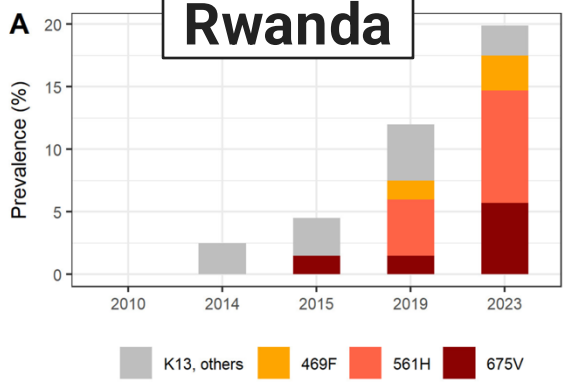
Eritrea



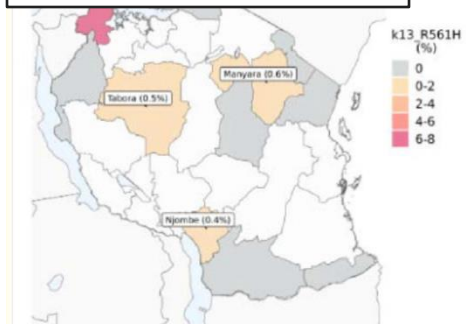
Central Africa



Rwanda

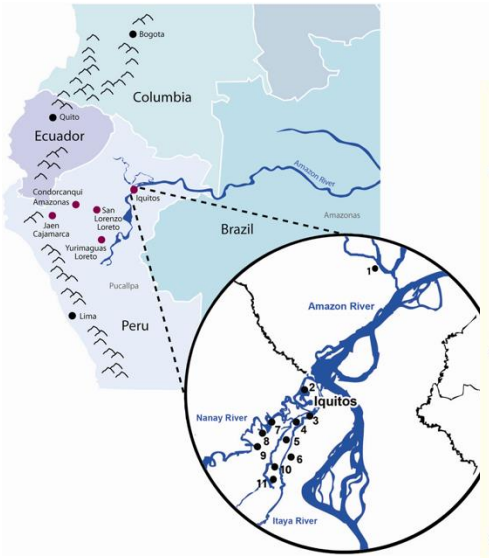


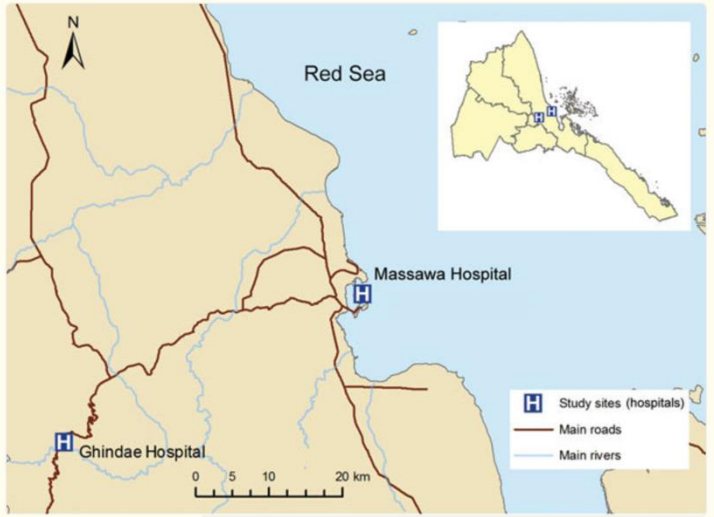
Tanzania

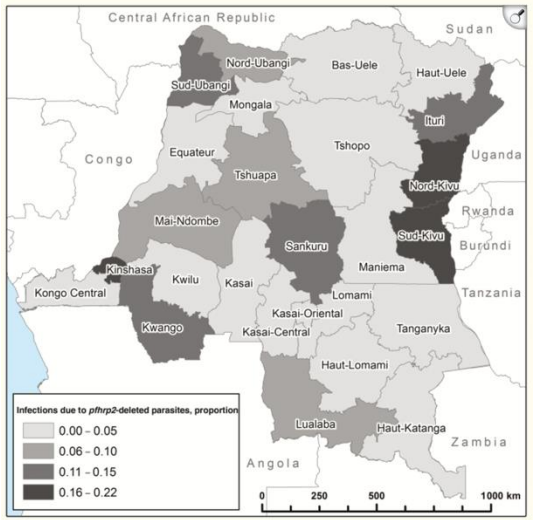


Identifying and quantifying *pfhrp2/3* deletions

- 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

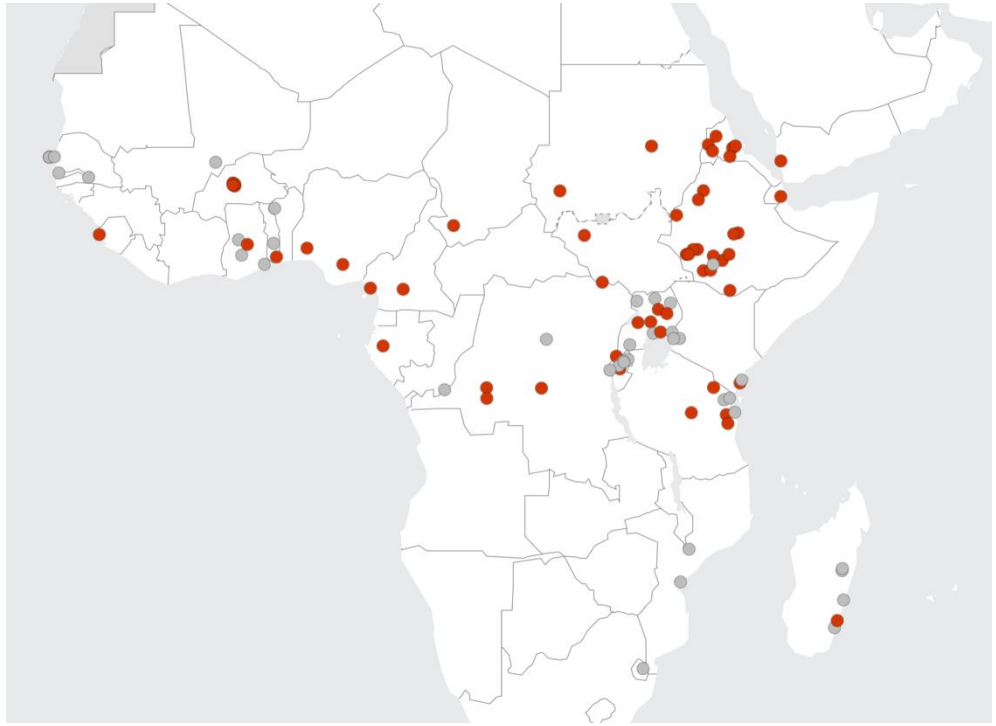


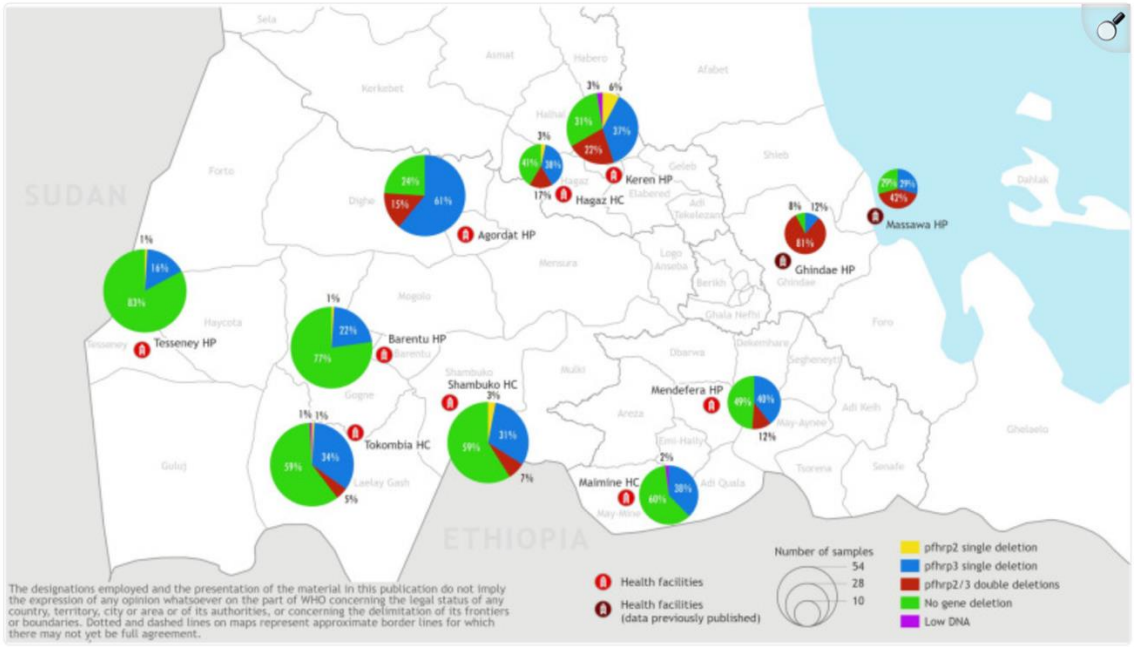




Identifying and quantifying *pfhrp2/3* deletions

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





Surveillance patterns in 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

Aims for the workshop

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