The Next-Gen in the Fight Against Malaria

translating genome science into
new tools for global health

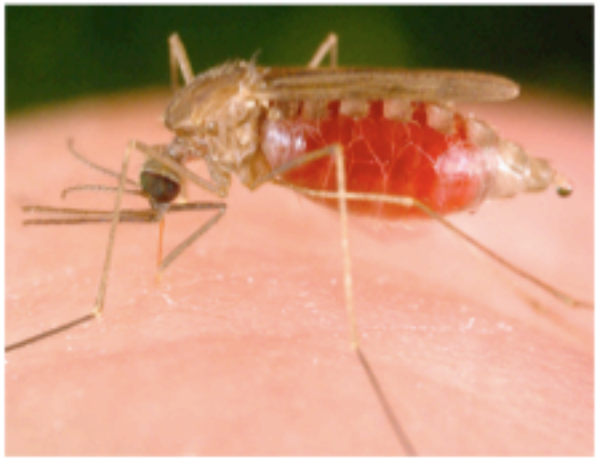
Bronwyn MacInnis
on behalf of the Malaria Genetics Team and
loads of other people at Sanger and abroad

Malaria…a tale of three genomes

Host

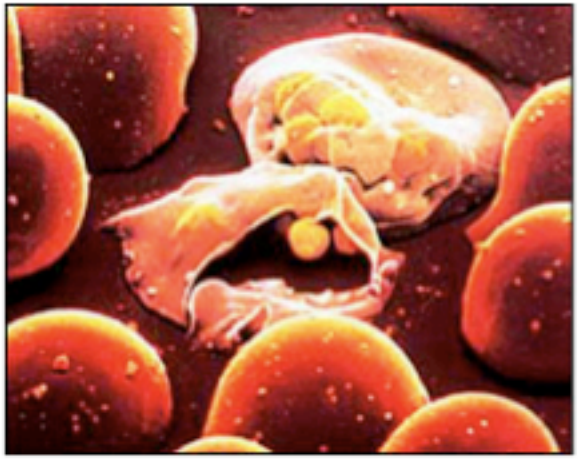
- Children under 5, pregnant women most at risk
- Acquired immunity kicks in at age ~5-8
- Non-exposed adults are susceptible

Vector



- Anopheles mosquitoes
- ~50 species transmit malaria

Parasite



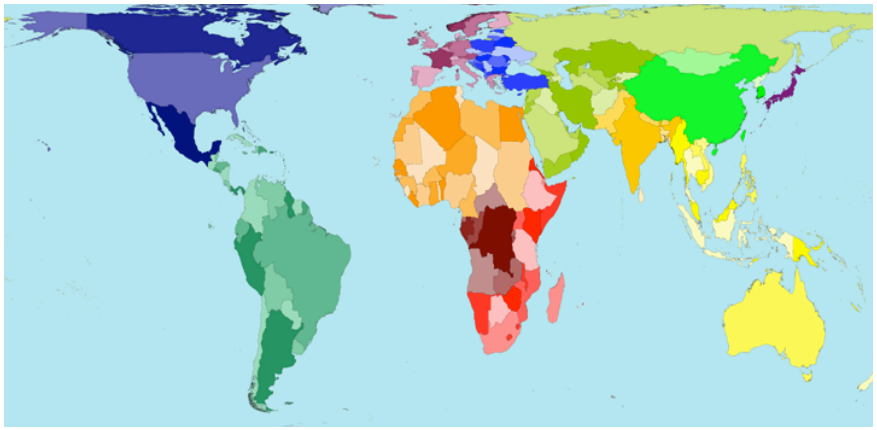
- Plasmodium parasites
- *P. falciparum* and 3.5 other species cause human malaria
- single cell eukaryotes

Some Scary Statistics

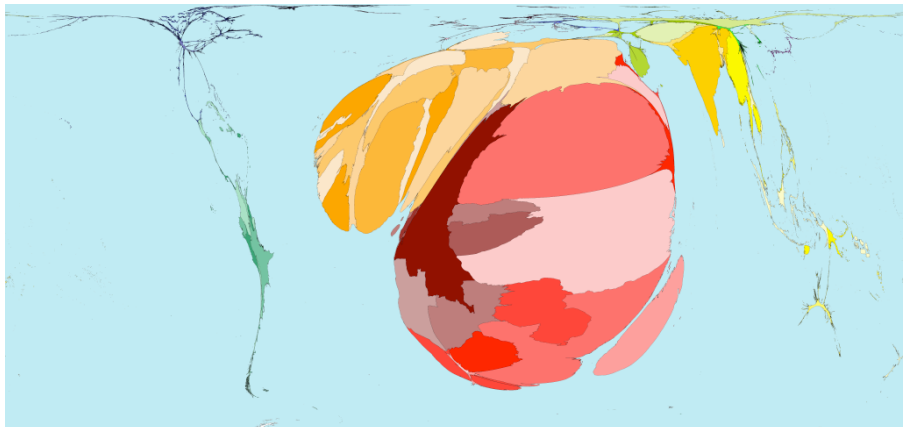
According to the World Health Organization (2008):

- 250 million cases of malaria worldwide
- 3.3 billion--half of the world's population--at risk
- leading cause of death in children under 5 in Africa… there a child dies every 45 seconds, >1m deaths each year
- direct economic cost of $15 billion USD/year

World Map by Landmass



Relative Global Burden of Malaria



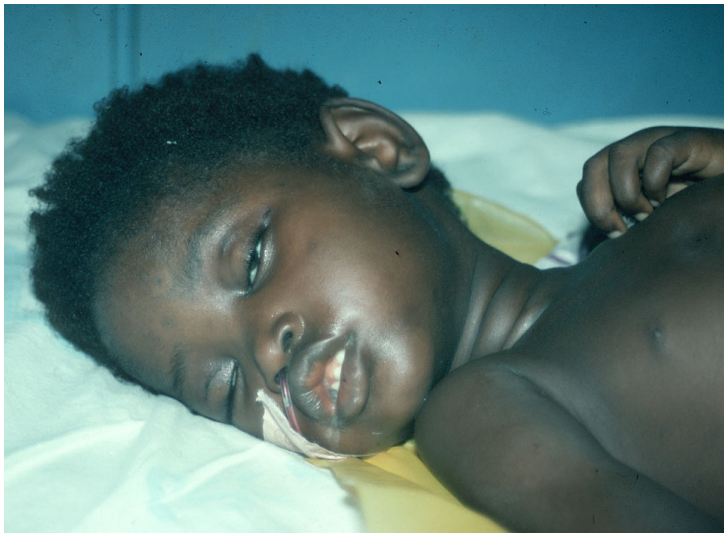
Malaria Illness

Acute symptoms

range from mild to severe…
fever
shivering
fatigue, pain
respiratory distress
anemia
retinal damage
convulsions
coma
death

Long term effects

brain damage
physical and cognitive impairment



Some kids die from malaria, some don't even get sick

The Malaria Life Cycle

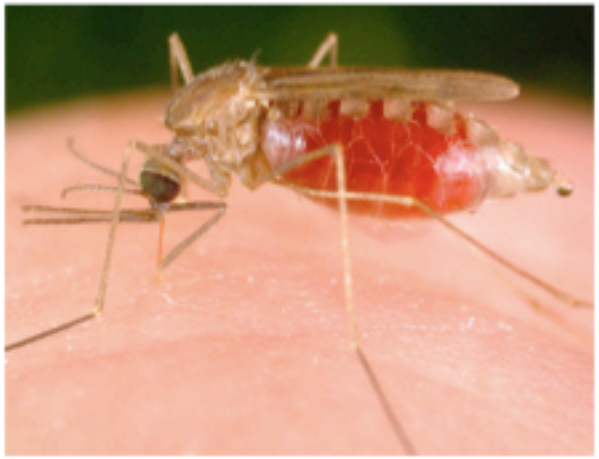
just show them the video, explains it way better than you would!

Malaria…a tale of three genomes

Host

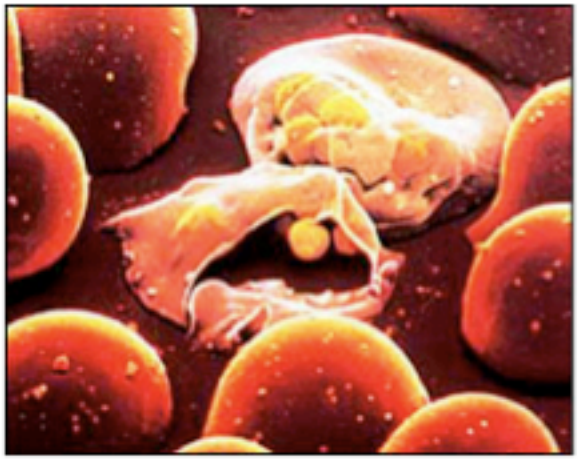
natural genetic resistance:
why some kids get malaria
and others don't

Vector



track transmission
and evolution of
insecticide resistance

Parasite



track outbreaks and evolution
of antimalarial drug resistance

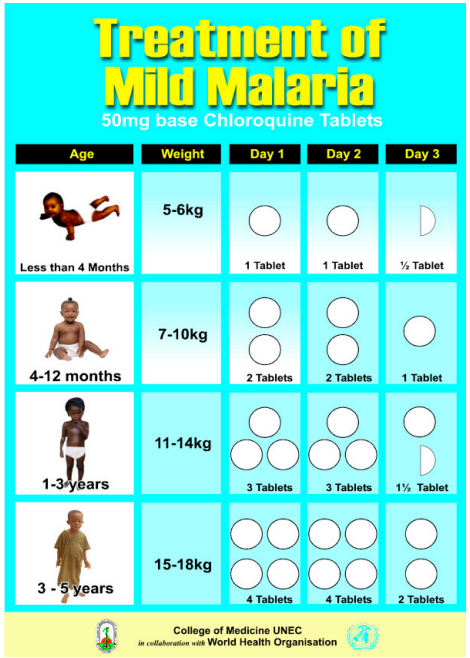
Our work in these organisms

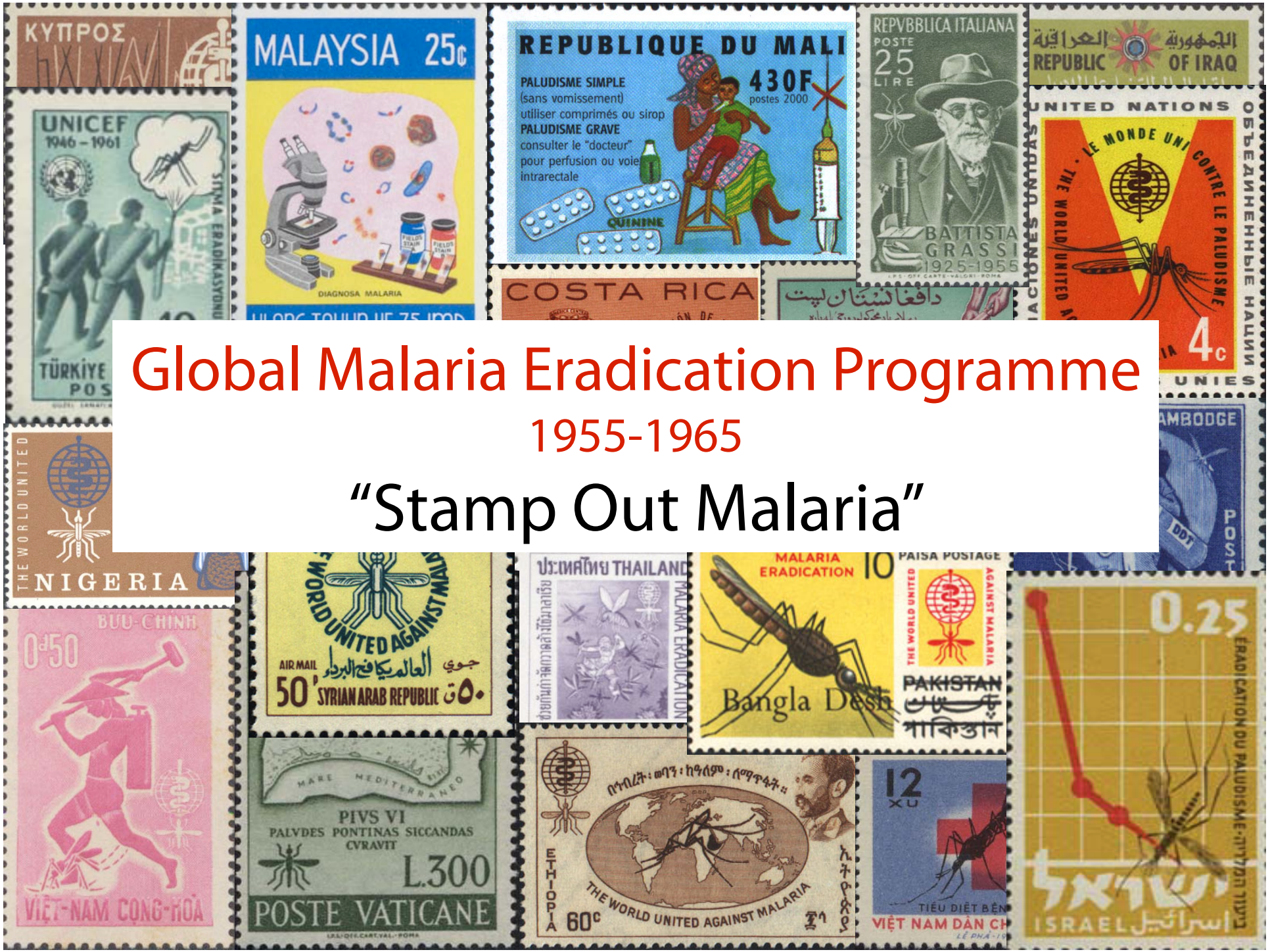
Malaria is a treatable and preventable disease

First Global Malaria Eradication Attempt
1955-1965

Potent insecticide
DDT

Effective antimalarial drug
Chloroquine
Cheap, safe, effective orally





Global Malaria Eradication Programme

1955-1965

"Stamp Out Malaria"

First Global Malaria Eradication Attempt
1955-1965

Potent insecticide
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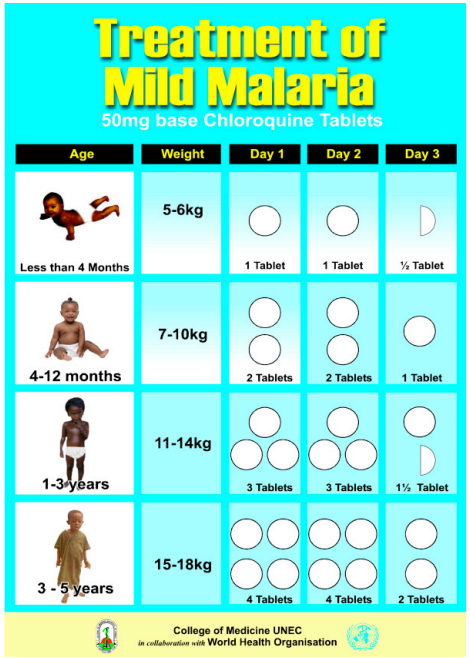
Effective antimalarial drug
Chloroquine
Cheap, safe, effective orally



First Malaria Eradication Attempt
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Potent inse

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Effective

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Cheap, safe, e

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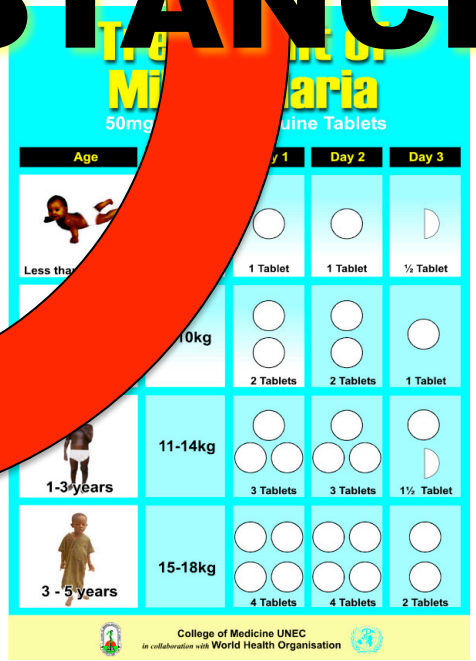
DRUG RESISTANCE



Fast forward to today…a second chance

Artemisinin

the new 'Silver Bullet' against malaria

Artemisia annua

- Chinese traditional medicine herb
- first described as an anti-malarial in 4 BC
- "discovered" by modern science in 1972/1982

Super Artemisinin!

Eliminate, the new Eradicate

GLOBAL MALARIA ACTION PLAN
for a malaria-free world

ROLL BACK MALARIA

Since 2007, a joint initiative of >500 other partners including WHO, UNICEF, UNDP, the World Bank and the Gates Foundation

Targets for **2015**

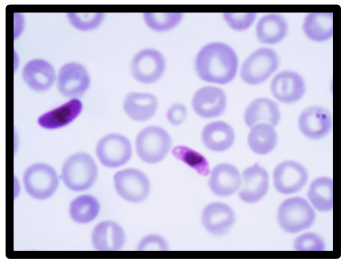
- Reduce malaria deaths to near zero
- Reduce malaria cases by 75% compared to 2000
- Eliminate malaria in 8-10 countries

Malaria Elimination Take 2

Why bother with genomics??

Tracking genome variation can provide effective system for global surveillance of the emergence and spread of anti-malarial drug, vaccine and insecticide resistance

positive blood smear



reading in malaria slides in Sri Lanka during first Global Malaria Eradication Campaign

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Fears for new malaria drug resistance

The drug resistance was first detected in Pailin province in western Cambodia

By Jill McGivering
BBC World Service, Cambodia

In a small community in Western Cambodia, scientists are puzzling over why malaria parasites seem to be developing a resistance to drugs - and fearing the consequences.

Ten days ago, Chhem Bunchhin, a teacher in Battambang Province, became ill with chills, fever, headache and vomiting.

At a nearby health centre he was treated with drugs

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Artemisinin Resistance in *Plasmodium falciparum* Malaria

Arjen M. Dondorp, M.D., François Nosten, M.D., Poravuth Yi, M.D., Debashish Das, M.D., Aung Phae Phyo, M.D., Joel Tarning, Ph.D., Khin Maung Lwin, M.D., Frederic Ariey, M.D., Warunee Hanpithakpong, Ph.D., Sue J. Lee, Ph.D., Pascal Ringwald, M.D., Kamolrat Silamut, Ph.D., Mallika Imwong, Ph.D., Kesinee Chotivanich, Ph.D., Pharath Lim, M.D., Trent Herdman, Ph.D., Sen Sam An, Shunmay Yeung, Ph.D., Pratap Singhasivanon, M.D., Nicholas P.J. Day, D.M., Niklas Lindegardh, Ph.D., Duong Socheat, M.D., and Nicholas J. White, F.R.S.

consequences.

Ten days ago, Chhem Bunchhin, a teacher in Battambang Province, became ill with chills, fever, headache and vomiting.

At a nearby health centre he was treated with drugs

TOP ASIA-PACIFIC STORIES

Our work in parasite (and vector) genetics

What's the goal?

Next Gen Sequencing Meets Disease Surveillance

Collect parasite samples and phenotype data from patients

↓

Sequence the DNA and analyze genome variation in their parasites

↓

Map genome variation and phenotype data in space and time
using open access, user friendly software to share the data

↓

Track disease features like drug resistance

↓

Inform public health decisions and policies

Beta Version

MapSeq/pf

plasmodium falciparum

beta release

What is MapSeq/pf?

MapSeq/pf is a database of genome variation in the malaria parasite *Plasmodium falciparum* in populations around the world, with data on 189 samples and growing. It allows you to browse the data for a geographical location or for a genomic region. You can take a high level view of population structure for a large group of samples, or you can zoom in to view the sequence data for an individual sample.

MapSeq/pf community

Malaria researchers around the world have contributed samples and data to the MapSeq/pf project. Many of the samples were obtained directly from the blood of individuals with malaria infection without culture adaptation. About the investigators and how you can participate >>

Next-generation sequencing

The genome variation data in MapSeq/pf have been produced at the Wellcome Trust Sanger Institute by next-generation sequencing. This

Enter MapSeq/pf

- **Open access**
- **Sign in for full functionality**

Explore MapSeq features

- Viewing genotyping data
- Exploring the alignment for the genotyping data
- Compare SNP genotypes for two groups of samples
- Population structure of a group of samples
- Geographical information about a sample

FAQs

- Key concepts (glossary)
- Requirementes and compatibility issues
- What is the accuracy of these SNP data?
- Why can't I access data on all of the samples?
- I can see SNPs but how do I find other sorts of genome variation?

Beta Version

Control Wizard Help Logout Guest

www.sanger.ac.uk/MapSeq/

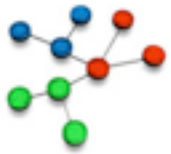
Available Tasks

Genotyping View

Choose one or more samples, and view their nucleotides at variable positions in any region of the genome (specific genes, chromosome segments, etc.). Compare mutations in different samples, and identify the present of phenotypically important variations.

Compare Groups

Define groups of samples, and view their nucleotides, identifying the variable positions where mutations are strongly associated with the grouping. Identify the genomic features that characterize a population, or a phenotypic trait.



Analyze Populations

Choose a number of samples, and conduct Principal Component Analysis (PCA) on their genotyping data- across the whole genome, or within specific genes or regions. Graphic visualization allows you to explore genomic similarity and differences between samples.

Browse Samples

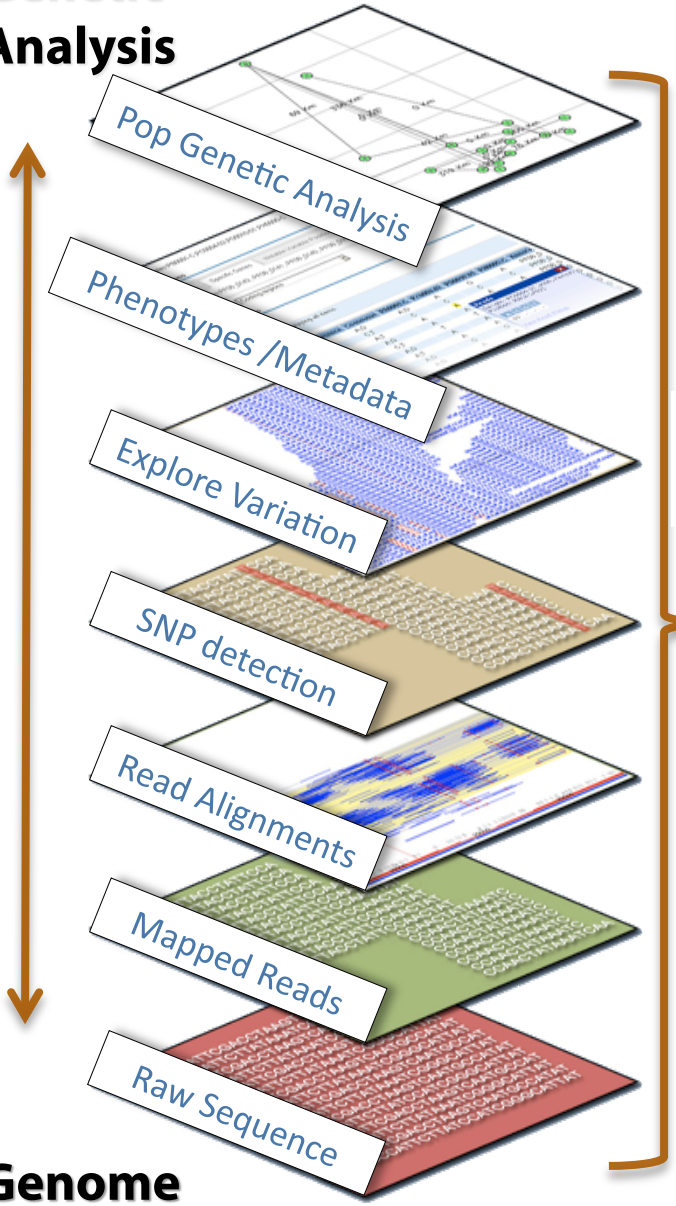
View information about the samples available in MapSeq: geographical information, study information, submitter information, etc.

Browse Studies

View information about all the studies that are using the MapSeq/pf platform. Here you can check the purpose of the studies, the associated samples, the collaborators and the principal investigator.

Project Workflow

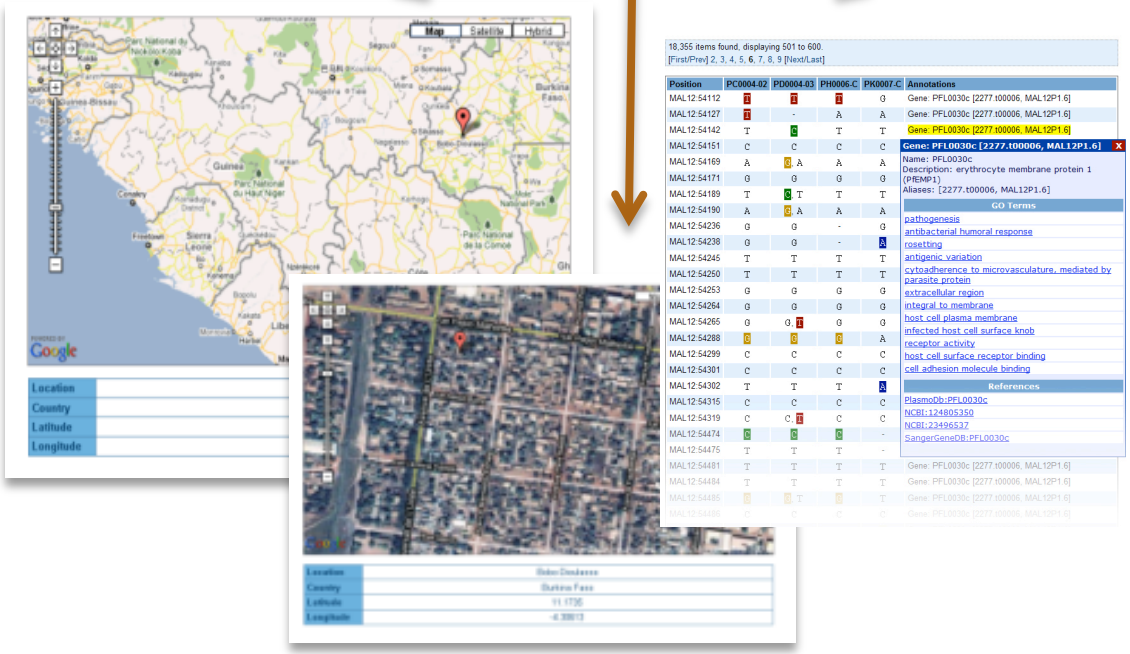
Population-level Genetic Analysis



Genome Sequence

MapSeq

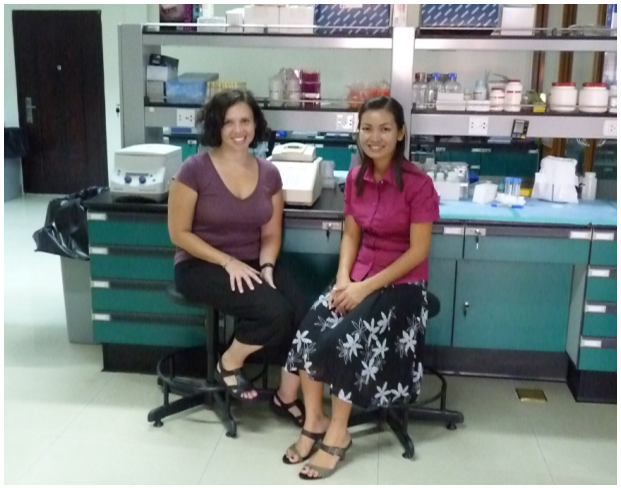
Geographical Mapping and Data Analysis



Sequencing clinical malaria samples is a big challenge

- we sequence what we get…samples are tiny, aren't cultured, often >90 % human
- each sample is precious
- field sites lack basic resources
- samples are typically mixed infections
- the *P. falciparum* genome is really tricky

Sequencing clinical malaria samples is a big challenge



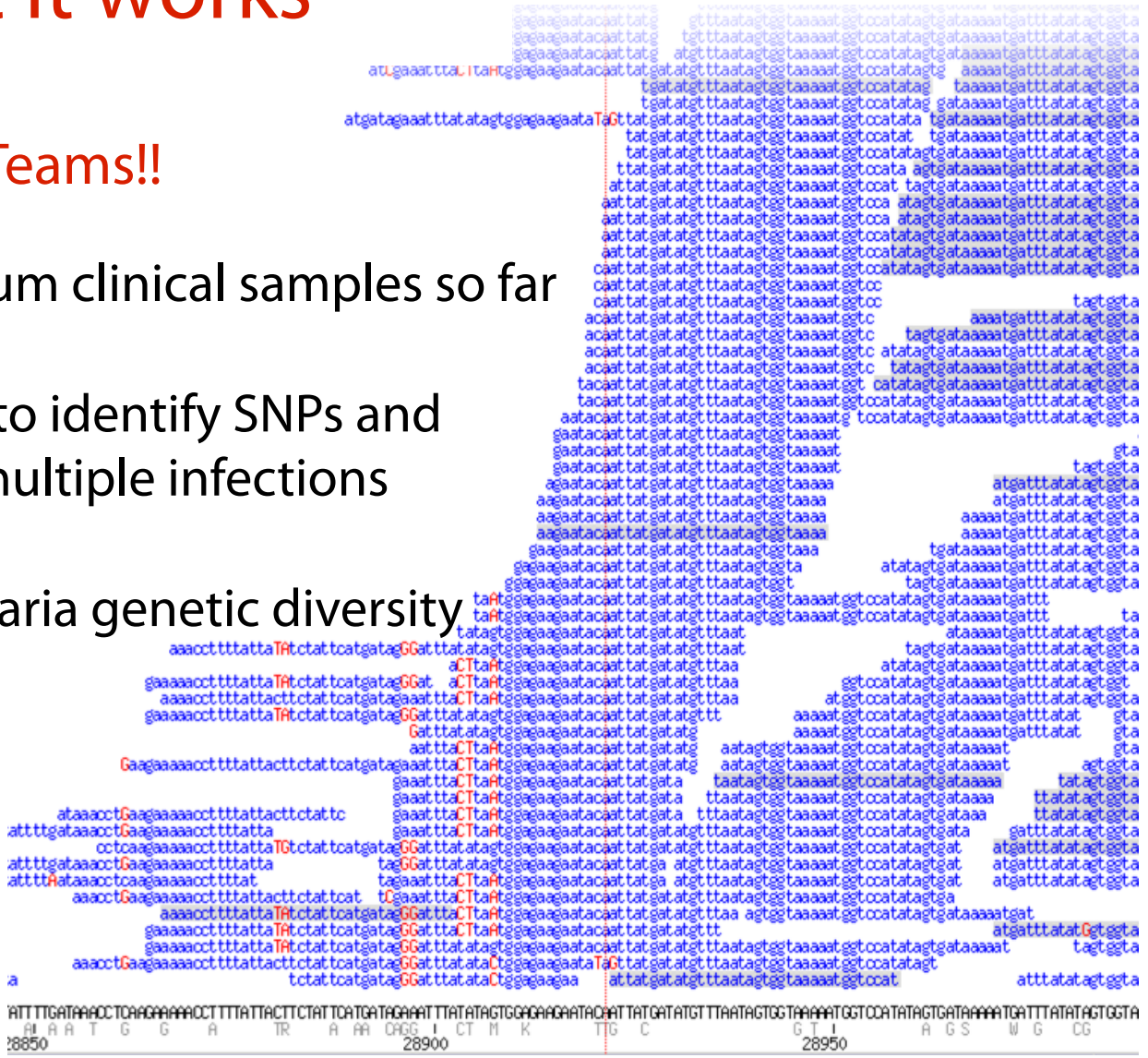
Working with partners to collect malaria samples in Cambodia

Sequencing clinical malaria samples is a big challenge

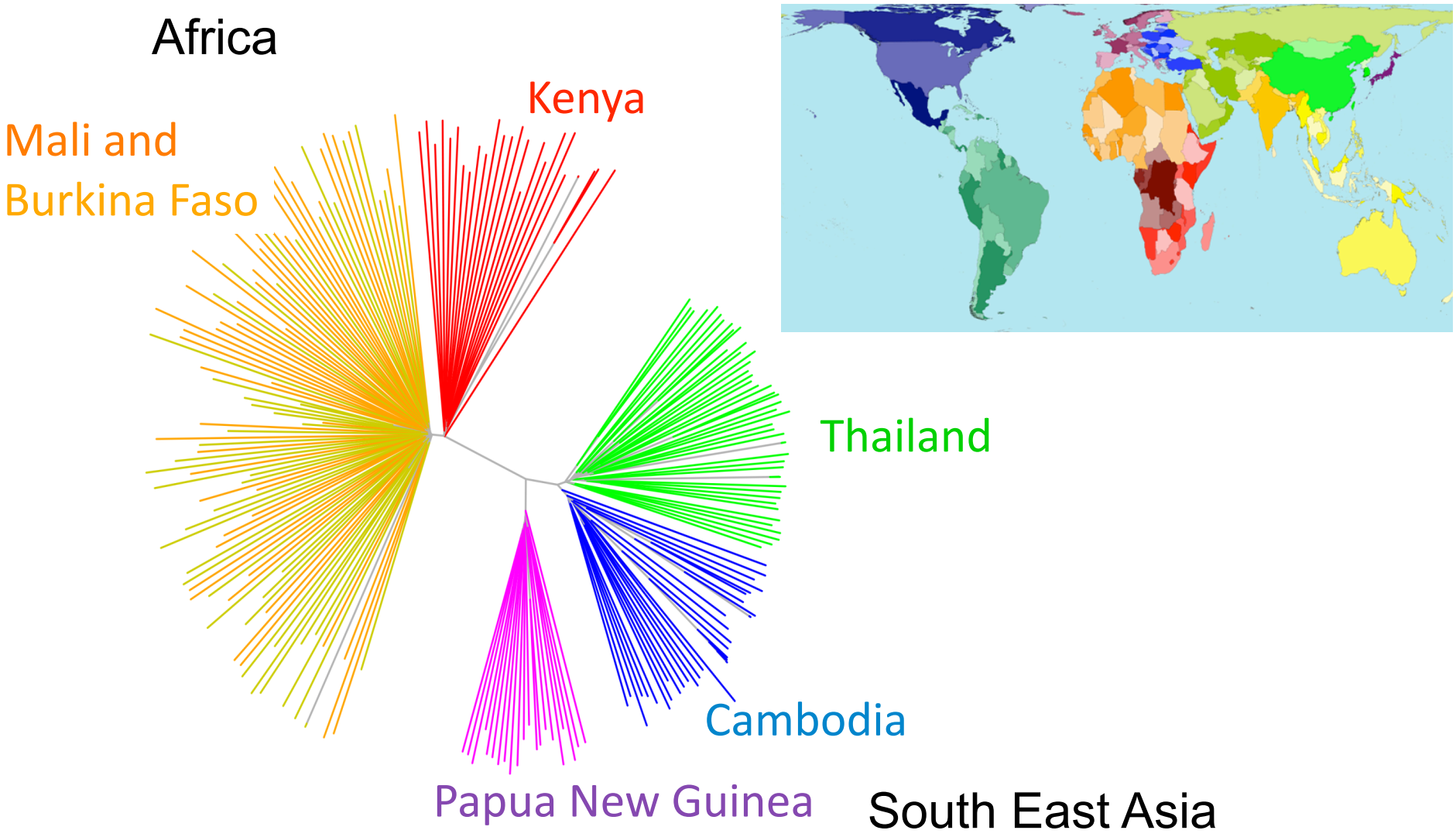
but it works

With huge thanks to the R&D,
Library Prep and Sequencing Teams!!

- sequenced ~1000 P. falciparum clinical samples so far
- established robust analyses to identify SNPs and other variants, and to detect multiple infections
- new insights into global malaria genetic diversity

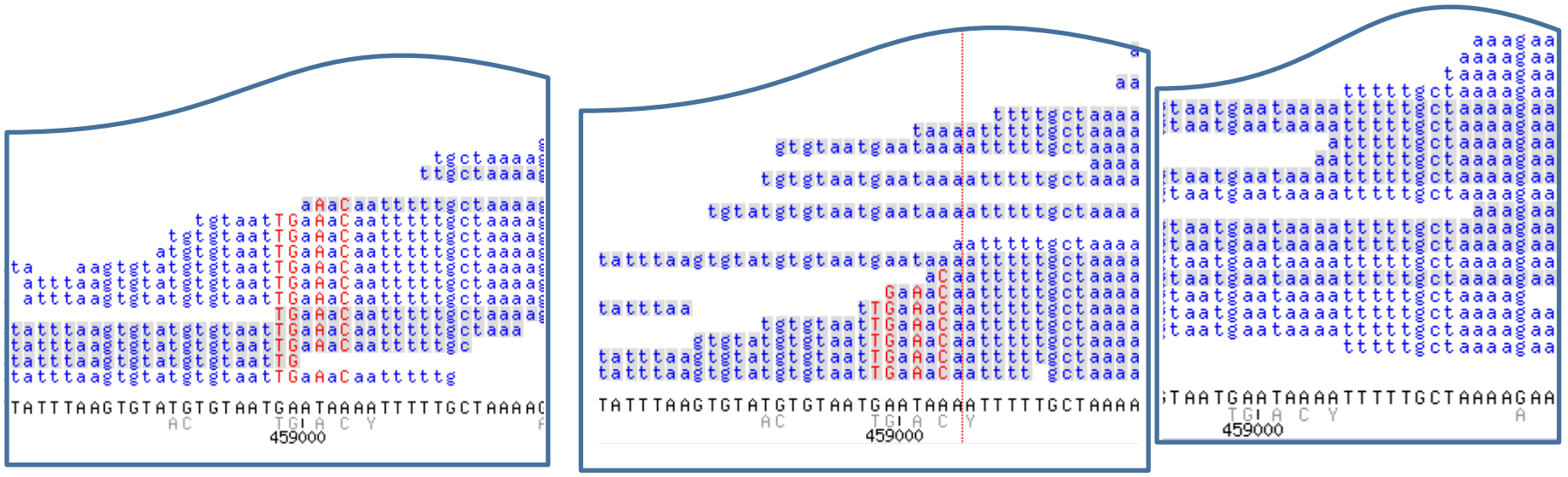


We can see patterns of global and regional population structure



We can detect known drug resistance mutations

Chloroquine resistance variant PfCRT K76T

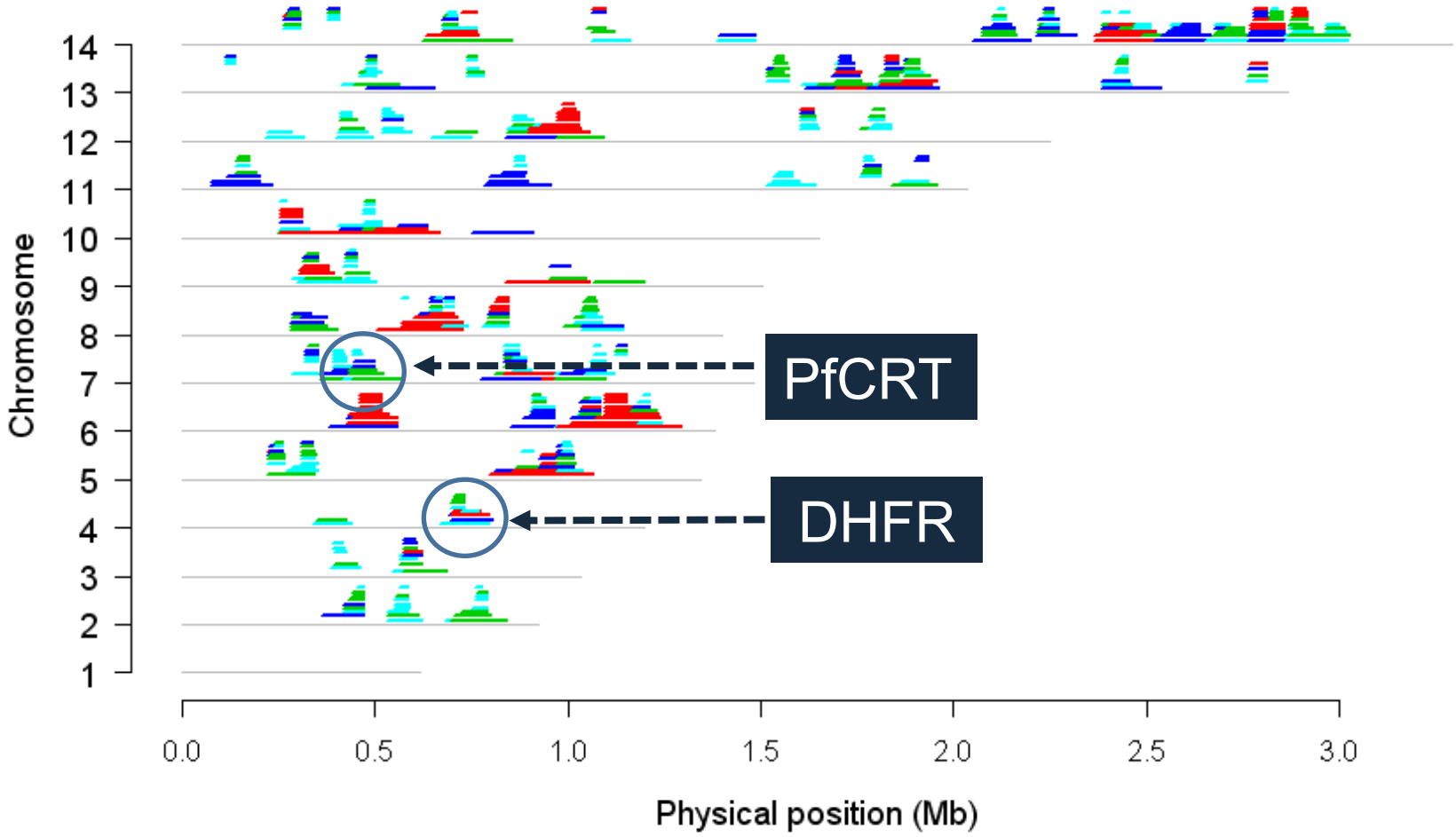


Thai isolate

Kenyan isolate

Malian isolate

We can detect signatures of recent evolutionary selection at known drug resistance genes …and novel loci



WWARN

Select treatment

Anti malarial:

Group:

- All Artemisinins
- All Non-Artemisinins

Component:

- Artemether (AM)
- Amodiaquine (AQ)
- Artesunate (AS)
- Atovaquone (AV)
- Chloroquine (CQ)
- Dihydroartemisinin (DA)
- Desethylamodiaquine (DQ)
- Doxycycline (DX)
- Lumefantrine (LF)
- Mefloquine (MQ)
- Pyrimethamine (P)
- Piperaquine (PQ)
- Quinine (QU)
- Sulfadoxine (S)
- Sulfadoxine-pyrimethamine (SP)

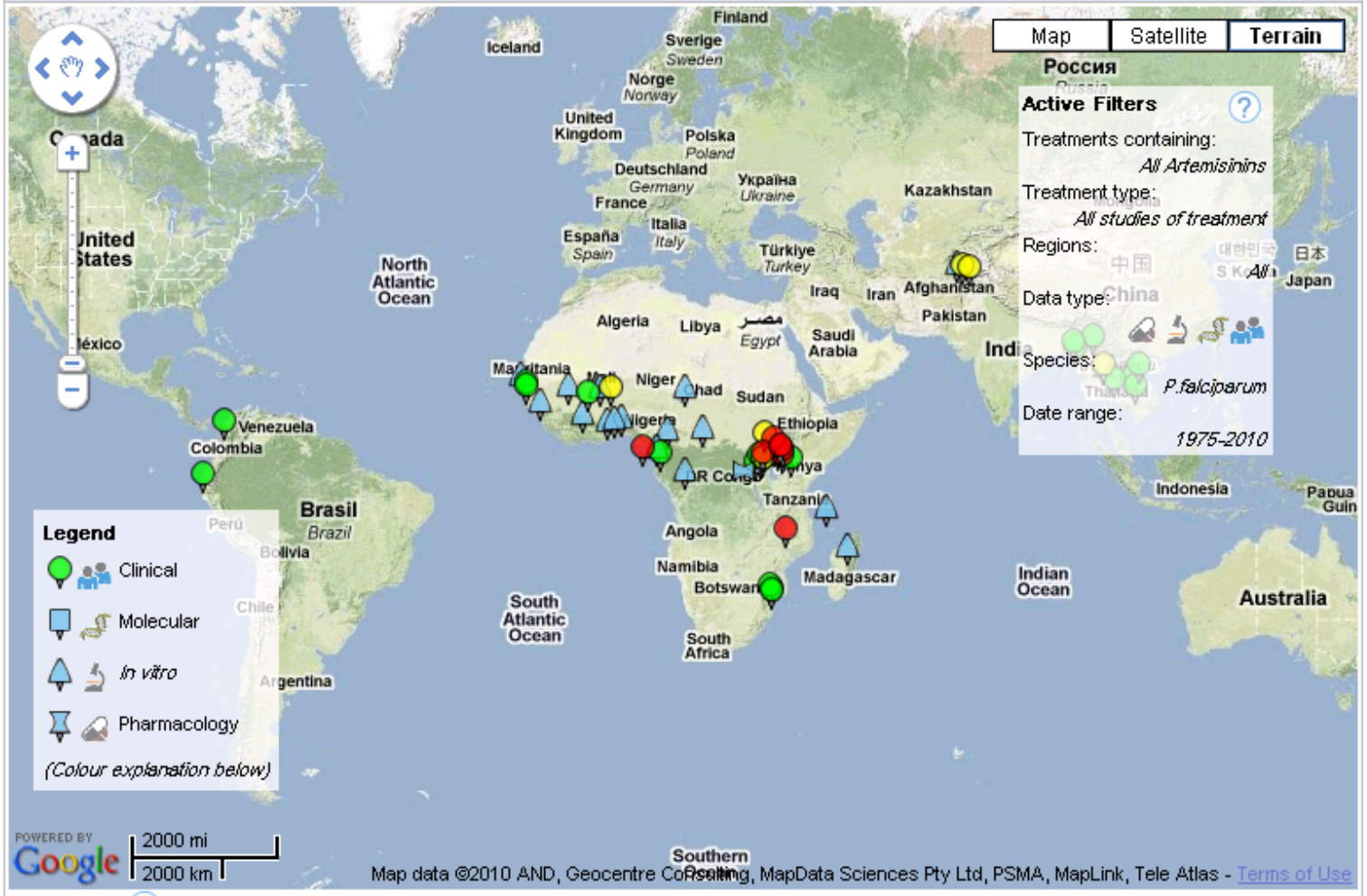
Limit to studies of:

All studies of treatment

Regions

- Americas
- Northern Africa
- Eastern Africa
- Central Africa
- Western Africa
- Southern Africa
- Western Asia
- South-Eastern Asia
- Southern Asia
- Melanesia

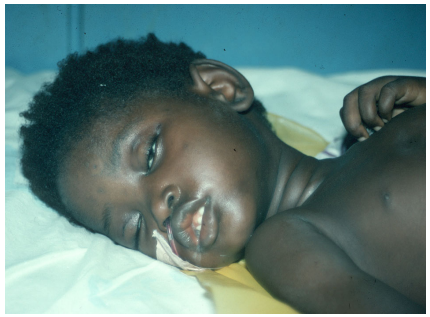
Map showing All Artemisinins data between 1975-2010



Year range : 1975 to 2010

1975 1980 1985 1990 1995 2000 2005 2010

Our work in host/human genetics



MalariaGEN
GENOMIC EPIDEMIOLOGY NETWORK

QUESTION: In communities where every child is repeatedly infected with malaria, why do some kids die and not others?

- With partners in >20 countries we have recruited ~13,000 cases of severe malaria and similar number of controls
- Published first Genome-Wide Association Study (GWAS) in African populations, of severe malaria in children in the Gambia*
- Identified signals in the human genome that may reveal how genetic differences can naturally protect some kids from malaria
- Useful information for vaccine design

*Jallow et al, *Nature Genetics* 41: 2009

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MalariaGEN

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  - Funders
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  - Local Projects
  - Data Access
  - Publications
- Ethics
  - Network Policies
  - Ethics Research
- Information
  - News
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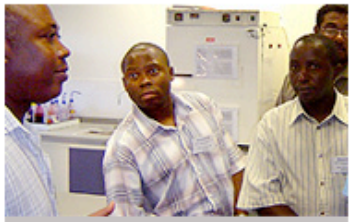
Network

Researchers in 21 countries, working together to apply new genome research tools to the problems facing malaria-affected communities.

Science

By discovering natural mechanisms of disease resistance, we aim to develop more effective ways of preventing malaria.



Ethics

Working in partnership with communities to address the ethical and social questions posed by advances in genome research.

New Doctoral Studentship in Ethics for 2011

The Ethox Centre has been awarded a major Wellcome Trust Enhancement Award to establish an international research network on the ethics of collaborative global health research. The network, which is a joint initiative of the Ethox Centre in Oxford and the Wellcome-KEMRI Unit in Kilifi, Kenya, will...

More >>

Other Stories

4th Nov 2010
In a study funded by the Wellcome Trust, geographers, biologists and statisticians at the University of Oxford,...

20th Sep 2010
The Wellcome Trust is going to host an Advanced Course entitled "Malaria Experimental Genetics". The aim is to...

6th Jul 2010
The aim of The Human Heredity and Health in Africa Project (H3Africa) is to support African scientists...

By "we" I mean….

The Sanger-Oxford Kwiatkowski Group

and…

MalariaGEN

GENOMIC EPIDEMIOLOGY NETWORK

Partner scientists and clinicians in >20 malaria endemic countries who share samples and data

Thanks A LOT to

Mandy Sanders
Matt Berriman
Chris Newbold
Julian Rayner
Oliver Billker
Gordon Dougan
Mike Quail
Dan Turner
Carol Churcher
Cordelia Langford
Jeff Barrett

And to all of the patients, especially sick children
and their parents, for supporting this work

And to you for listening—thank you!