Treatment of Uncomplicated Malaria in the wake of Multi-drug Resistant Falciparum Malaria

Ben Andagalu, MD M.Sc. (Clinical Trials)

KEMRI/Walter Reed Project

Outline

- Introduction
- Malaria drug resistance – current status
- Strategies to delay emergence of resistance

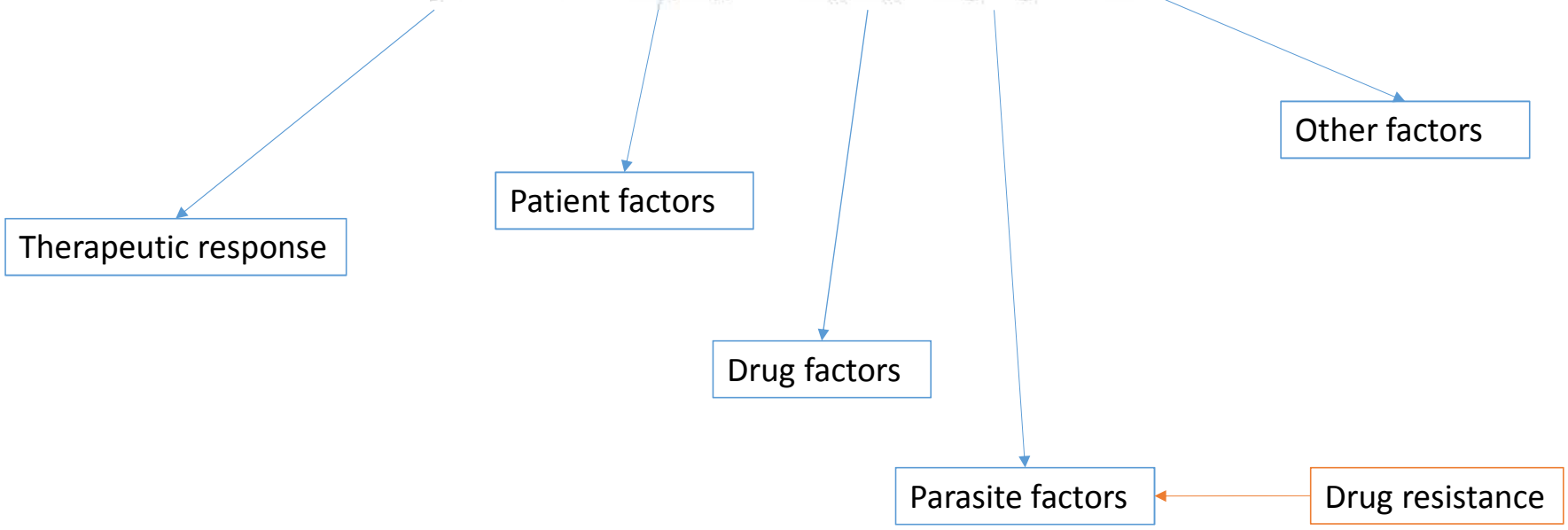
Introduction

- The World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) for treating uncomplicated Plasmodium falciparum malaria
- The increasing availability of ACTs and long-lasting insecticidal nets (LLINs) over the last decade has contributed to a substantial reduction in malaria morbidity and mortality in Sub-Saharan Africa
- However, the reduced efficacy of artemisinin against Plasmodium falciparum malaria in the Greater Mekong region threatens to jeopardize the recent gains in malaria control and elimination
- For combination therapies, the early parasitological response is determined largely by the artemisinin component.
- To prevent recrudescence, the malaria parasites that remain after exposure to the artemisinin component for two 48-hr asexual cycles must be cleared by the slowly eliminated partner drug
- Therapeutic responses are mainly determined by density and susceptibility of the infecting malaria parasites and drug exposure, although acquired host immunity can compensate for failing treatments.

Therapeutic response vs. drug resistance

$$y = a + bx + e$$

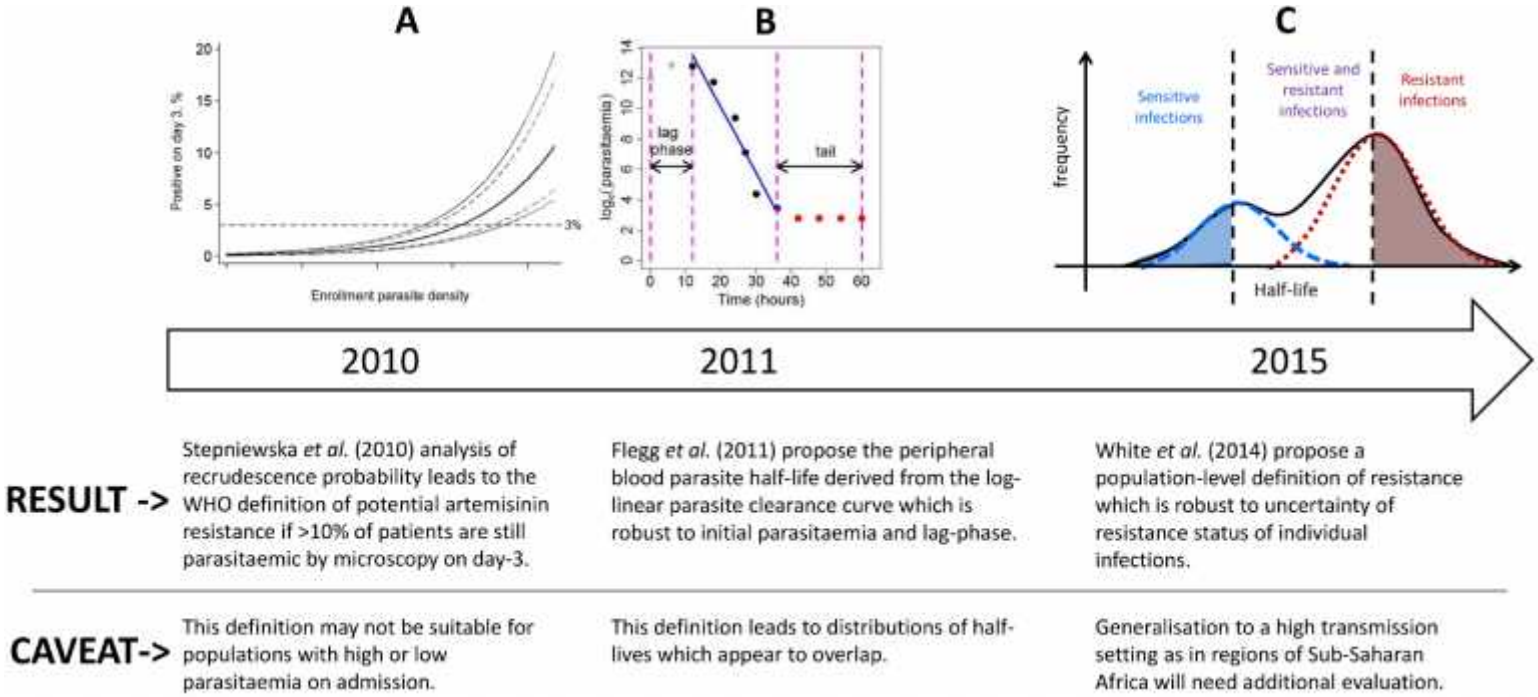
$$y = a + b_1x_1 + b_2x_2 + b_3x_3 + e$$



Drug resistance – evolving definition

- The ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject (WHO 1967)
- The drug must *"gain access to the parasite or the infected red blood cell for the duration of the time necessary for its normal action"* (Bruce-Chwatt et al, 1986)
- Artemisinin resistance is defined as delayed parasite clearance following treatment with an artesunate monotherapy, or after treatment with an artemisinin-based combination therapy (ACT). Such resistance represents partial resistance (WHO 2015)
  - *suspected artemisinin resistance* – defined as a high prevalence of the delayed parasite clearance phenotype, or high prevalence of K13 mutants;
  - *confirmed artemisinin resistance* – defined as a combination of delayed parasite clearance and K13 resistance-associated mutations in a single patient.

Drug resistance – evolving definition



White et al. PLOS Medicine | DOI:10.1371/journal.pmed.1001823

Biochemical mechanism of resistance

- Chloroquine inhibits the polymerization of haem, a toxic by-product of HgB digestion.
  - It is believed that resistance of *P. falciparum* to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of haem polymerization
  - PfCRT mutation is the genetic signature
- Pyrimethamine and related compounds inhibit the folate synthesis step mediated by dihydrofolate reductase (DHFR) while sulfones and sulfonamides inhibit the step mediated by dihydropteroate synthase (DHPS)).
  - Specific gene mutations encoding for resistance to both DHPS and DHFR
- Atovaquone acts through inhibition of electron transport at the cytochrome *bc1* complex.
  - Although resistance to atovaquone develops very rapidly when used alone, when combined with a second drug, such as proguanil (the combination used in MalaroneTM) or tetracycline, resistance develops more slowly.
  - Resistance is conferred by single-point mutations in the cytochrome-b gene
- Genome wide association studies (GWAS) have revealed parasite genetic loci associated with artemisinin resistance (K13). However, there is no consensus on biochemical targets of artemisinin.

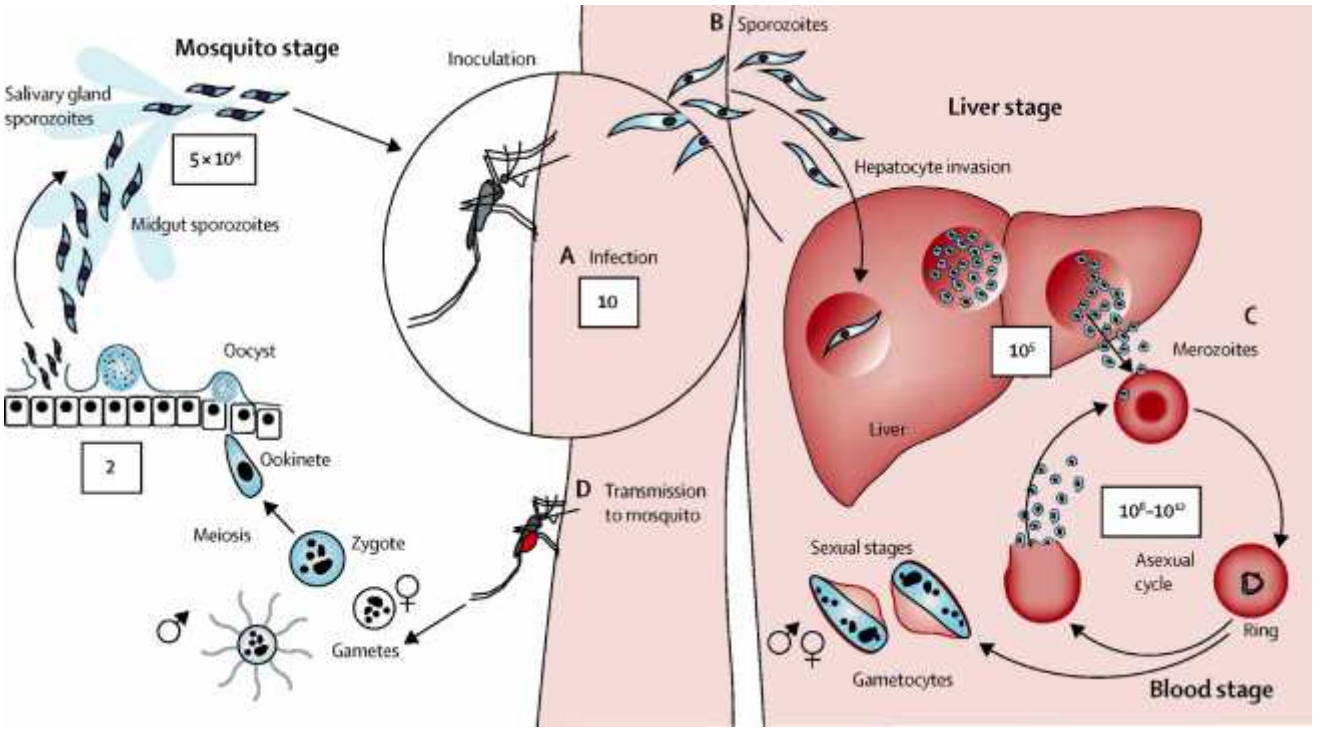
Bloland. WHO/CDS/CSR/DRS/2001.4;
Cui et al. Am. J. Trop. Med. Hyg.,
93(Suppl 3), 2015, pp. 57–68;

Emergence and spread of resistance

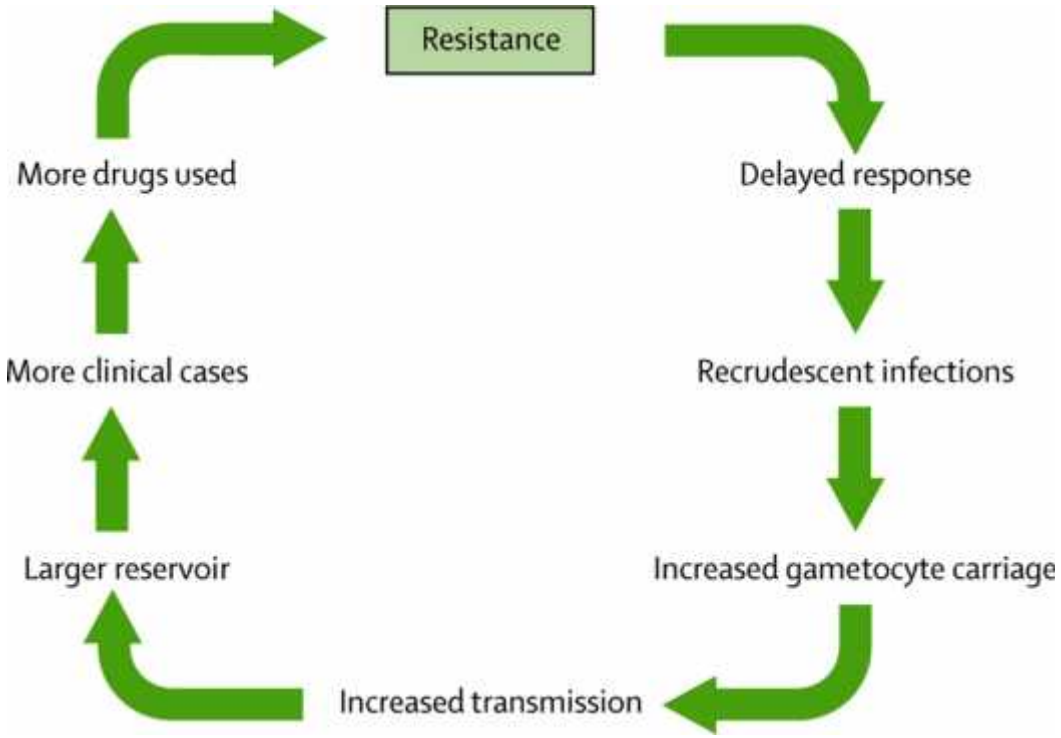
- Phase I: An initial genetic event produces a resistant mutant (de novo mutation); the new genetic trait gives the parasite a survival advantage against the drug
- Phase II: The resistant parasites are selected for and begin to multiply, eventually resulting in a parasite population that is no longer susceptible to treatment
- The propagation of newly emerged resistance depends on the recrudescence and subsequent transmission of an infection that has generated a de novo resistant malaria parasite.

White. J. Clin. Invest. 113:1084–1092 (2004). doi:10.1172/JCI200421682

Life cycle vs resistance



Spread of resistance



Talisuna et al. Lancet Infect Dis 2012;12: 888–96

Factors influencing the spread of resistance

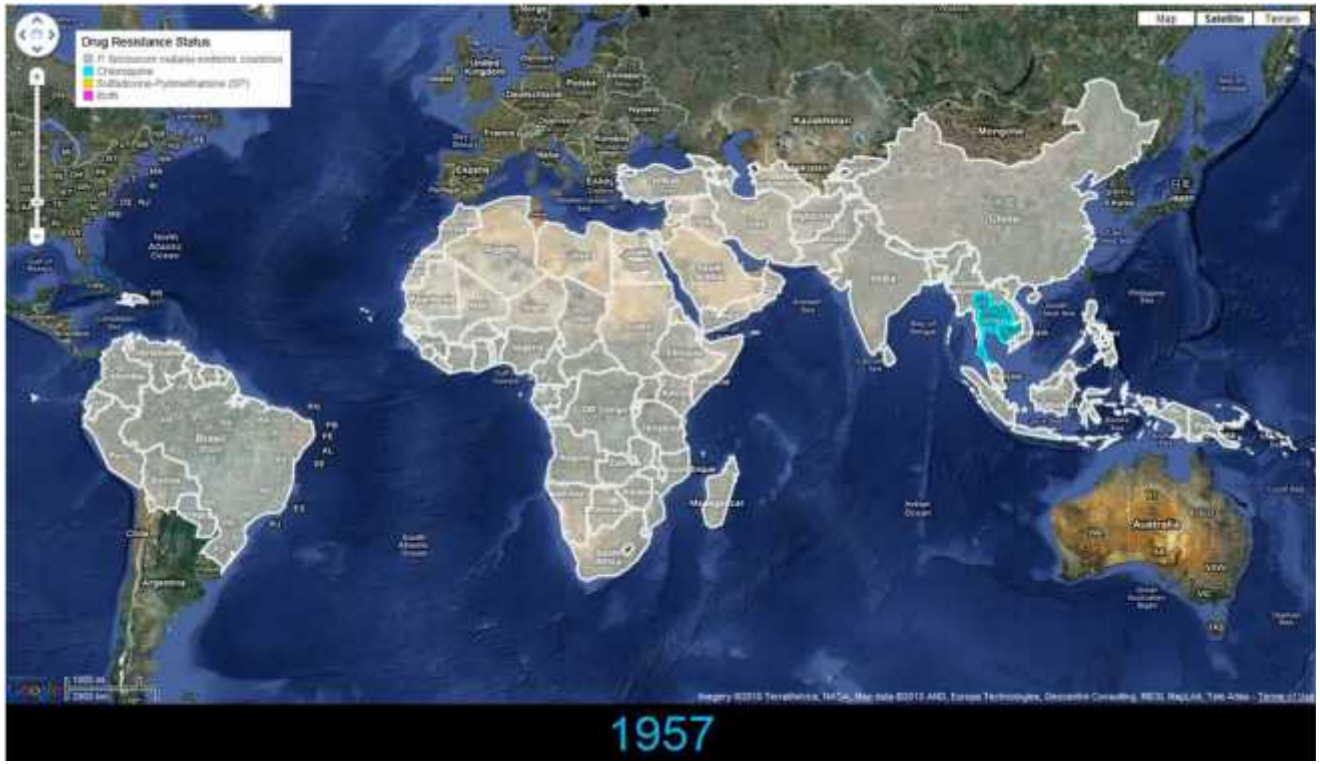
- Biological
  - Host immunity
  - Characteristics of recrudescent infections
  - Vector-parasite combinations
  - Cross-resistance
  - Prolonged elimination periods
- Programmatic
  - Overall drug pressure
  - Inadequate drug intake
  - pK and pD properties

Bloland. WHO/CDS/CSR/DRS/2001.4

Detection of resistance

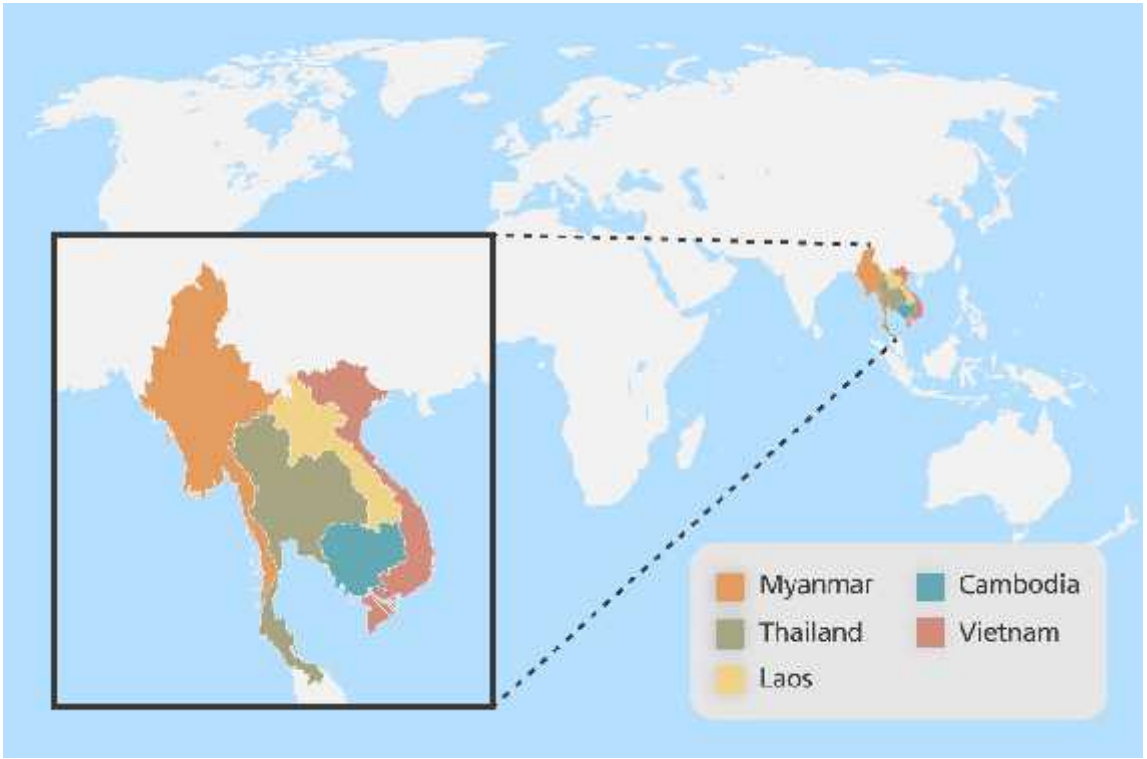
- *In vivo* tests
  - Reflect actual epidemiological situations
  - Affected by patient factors (host immunity, drug absorption), misclassification of reinfections as recrudescence
- *In vitro* tests
  - More accurately reflect pure resistance
  - Culture adaptation may result in different parasite population
- Molecular characterization
  - PCR techniques to detect genetic mutations
- Animal model studies
  - Essentially *in vivo* test in non-humans

Historical perspective – CQ and SP



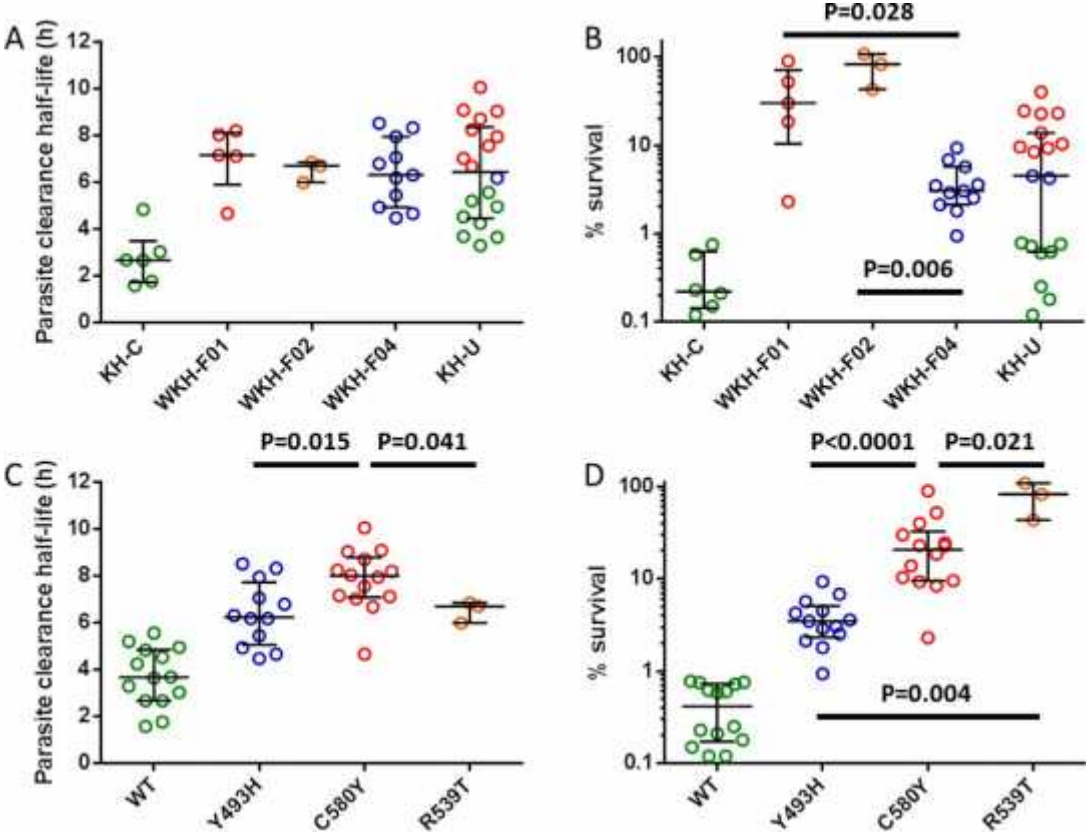
http://www.wwarn.org

Artemisinin resistance distribution



www.yourgenome.org

K13 mutations, RSA findings

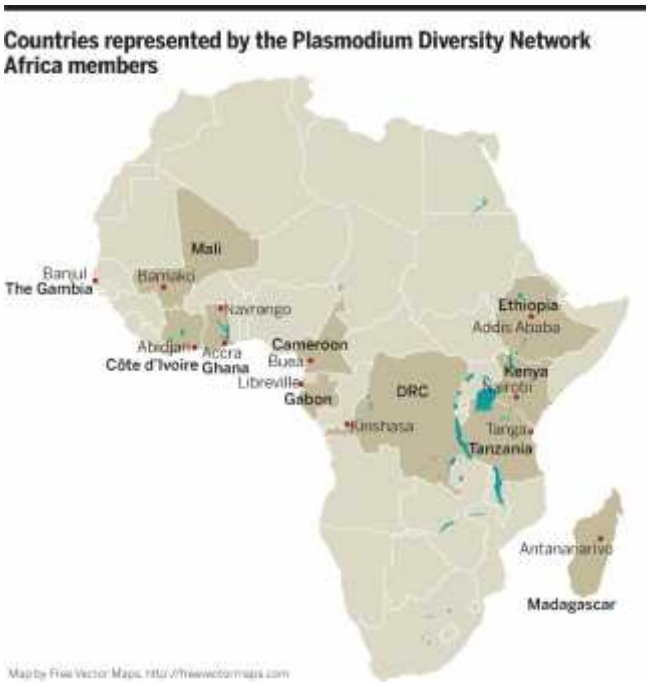


Chanaki Amaratunga et al. Antimicrob. Agents Chemother. 2014;58:4935-4937

K13 mutation	Classification
441L	Associated
446I	Associated
449A	Associated
458Y	Associated
493H	Confirmed
539T	Confirmed
543T	Confirmed
553L	Associated
561H	Associated
568G	Associated
574L	Associated
580Y	Confirmed
675V	Associated

WHO/HTM/GMP/2015.4

K13 polymorphisms in Africa



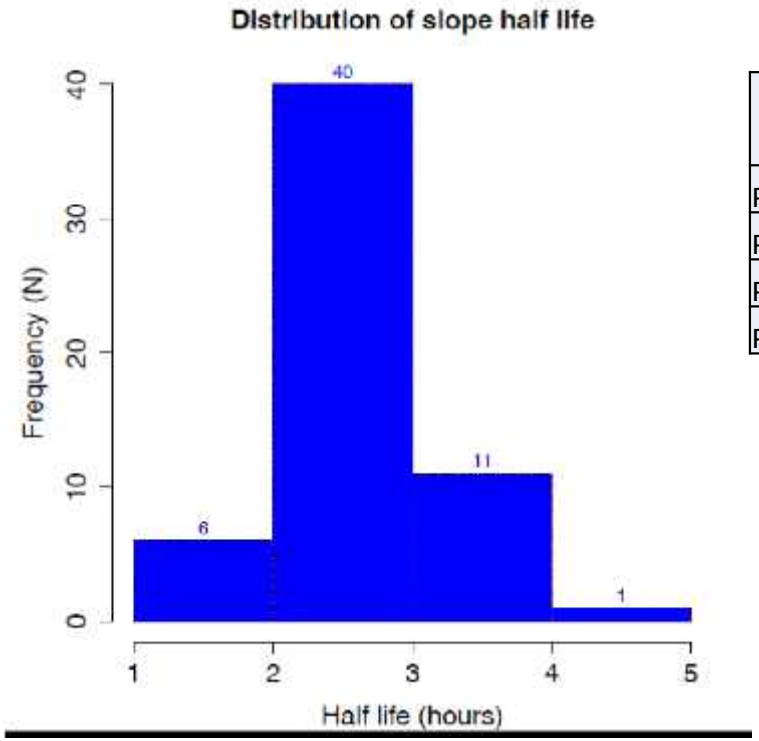
Anita Ghansah et al. Science 2014;345:1297-1298

K13-Propeller Polymorphisms in *Plasmodium falciparum* Parasites From Sub-Saharan Africa

Edwin Kamau,[1] Susana Campino,[2] Lucas Amenga-Etego,[4] Eleanor Drury,[2] Deus Ishengoma,[6] Kimberly Johnson,[3] Dieudonne Mumba,[7] Mihir Kekre,[2] William Yavo,[8] Daniel Mead,[2] Marielle Bouyou-Akotet,[9] Tobias Apinjoh,[10] Lemu Golassa,[11] Milijaona Randrianarivelojosia,[12] Ben Andagalu,[1] Oumou Maiga-Ascofare,[13,15] Alfred Amambua-Ngwa,[14] Paulina Tindana,[4] Anita Ghansah,[5] Bronwyn MacInnis,[2] Dominic Kwiatkowski,[2,3] and Abdoulaye A. Djimde[2,13]

The Journal of Infectious Diseases 2015;211:1352-5

AL efficacy findings - Kisumu



	Median	Range
PC50	7.4	(0.8, 15.5)
PC90	12.7	(4.5, 21.7)
PC95	15.2	(6.5, 24.9)
PC99	21.2	(10.4, 32.3)

Treatment outcome	ACPR Before PCR correction	ACPR After PCR correction
D28	32/51 (62.8%)	51/51 (100%)
D42	21/48 (43.8%)	48/48 (100%)

Drug	Median IC50, nM (IQR)
Artemether	4.13 (1.68, 10.75)
Dihydroartemisinin	8.34 (1.84, 35.21)
Lumefantrine	31.69 (3.40, 111.49)

Preliminary data, TES study. PI- Andagalu, B

Hard facts

1. Antimalarial drugs will continue to be needed for the foreseeable future
2. As long as drugs are used, there is the chance that resistance will develop
3. Rate of development of resistance >rate of development of new drugs
4. Cost of strategies to counter drug resistance is an important factor to consider in Africa
5. Outside the Greater Mekong region, treatment failure with AL appears to be uncommon and is not necessarily due to drug resistance.
    - Other factors such as non-compliance with treatment schedule, poor drug quality, under dosing and drug–drug interactions contribute to treatment failure.

What needs to be done

- Rational use of malaria drugs
- Increased monitoring of antimalarial drug efficacy and resistance
- Use of molecular markers to identify genetic mutations related to antimalarial drug resistance in the parasite genome
- Use of gametocidal drugs for the reduction of malaria transmission
- Attainment of additional pharmaceuticals
- Use of multiple first line treatments

MFTs

- Multiple simulation models show that Multiple First Line Treatments (MFT) delays the emergence and spread of drug resistance
- MFT comes with higher program costs
- MFT could be socially beneficial but only for new products with unique dosing or adherence benefits
- Implementation can be a challenge
- MFT requires a balanced viewpoint from multi-stakeholders
- More studies that closely monitor the emergence and spread of resistance in countries that have recently started MFT are needed to strengthen the evidence base on MFT

Thank you